OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2022, Vol. 18, Number 3

ISSN 2450–1654
e-ISSN 2450–6478

VIA MEDICA

Oncology in Clinical Practice 2022, Vol. 18, Number 3, 139–209

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology

https://journals.viamedica.pl/oncology_in_clinical_practice

Oncology in Clinical Practice (ISSN 2450–1654, e-ISSN 2450–6478) is published six times a year by

VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80–180 Gdańsk, Poland
Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl,
http://www.viamedica.pl

21-0532.003.001

Editorial Address

Klinika Nowotworów Płuca i Klatki Piersiowej
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa, Poland
Phone: (+48 22) 546 21 69
e-mail: sekretariat4@pib-nio.pl

Indexed in Index Copernicus (ICV 2020 = 97.15), Ulrich's Periodicals Directory and CAS.

According to the statement of the Polish Ministry of Education and Science publication in the journal has been awarded with 100 points.

Editorial policies and author guidelines are published on journal website: http://journals.viamedica.pl/oncology_in_clinical_practice

ONCOLOGY
IN CLINICAL PRACTICE
Official Journal of the Polish Society of Clinical Oncology
https://journals.viamedica.pl/oncology_in_clinical_practice 2022, Vol. 18, Number 3

VIA MEDICA

ORIGINAL ARTICLE

Paulina Terlecka[1], Paweł Krawczyk[1], Kamila Wojas-Krawczyk[1], Anna Grenda[1], Izabela Chmielewska[1], Robert Kieszko[1], Artur Bartczak[2], Janusz Milanowski[1]

[1]Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland
[2]Department of Pathomorphology, Specialist Hospital for Lung Diseases "The rebirth" of the name of Klara Jelska in Zakopane, Poland

Different *MET* gene alterations in lung adenocarcinoma patients

Address for correspondence:
Paulina Terlecka, MD
Department of Pneumology, Oncology, and Allergology, Medical University of Lublin
Jaczewskiego 8, 20–954 Lublin
tel. +48 81 724 42 93
e-mail: paulina.chwil@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0019

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. In this study, we attempted to detect selected abnormalities in the *MET* gene using various molecular techniques.

Material and methods. Twenty-six lung adenocarcinoma patients had a diagnosis of abnormalities in the genes: *EGFR*, *ALK*, *ROS1*, *MET*, and *RET.* They were diagnosed using various techniques and assessment of PD-L1 expression using immunohistochemistry. Copy number variation of *MET* gene was assessed by qPCR and FISH techniques, *MET* exon 14 mutation by RT-PCR method, and *MET* mRNA expression by the RT-qPCR technique. Statistical analyses were performed using Statistica v. 13.1 and MedCalc 15.8.

Results. Most patients (57.7%) had a high *MET* gene copy number in the qPCR method, which was not confirmed by the FISH method. A significant positive correlation ($R = +0.573$, $p = 0.0022$) between the *MET* gene copy number assessed with the qPCR method and the relative *MET* mRNA expression was found.

Conclusions. The positive correlation between the *MET* mRNA expression and the *MET* gene copy number in the qPCR test indicates that these methods could complement each other. The performance of these two tests simultaneously increases the reliability of the *MET* gene assessment.

Key words: *MET* gene, adenocarcinoma, lung cancer

Oncol Clin Pract 2022; 18, 3: 139–146

Introduction

The *MET* gene is a proto-oncogene, and it encodes the hepatocyte growth factor receptor (HGFR). The binding of its ligand, hepatocyte growth factor, induces dimerization and activation of the receptor. This activates the downstream RAS/ERK/MAPK, PI3K/AKT, and Wnt/β-catenin signaling pathways, which play a role in cellular survival, embryogenesis, cellular migration, invasion, angiogenesis, and the epithelial to mesenchymal transition (EMT) [1].

Abnormalities of the *MET* gene are one of the most frequently identified genetic disorders in neoplastic diseases. Germline mutations in the *MET* gene have been found in hereditary papillary renal carcinoma (HPRC). Somatic *MET* mutations have been observed in sporadic papillary renal cell carcinoma, head and neck squamous cell carcinoma, and childhood hepatocellular carcinoma. Amplification and overexpression of this gene are also associated with multiple human cancers. The *MET* gene is altered in 5% of non-small cell lung cancer (NSCLC) patients. Alterations in exon 14 of the *MET* gene are detected in 3–4% of lung adenocarcinoma patients. The prevalence of *de novo MET* amplification in NSCLC ranges from 1% to 5% of patients, depending on the assay and the positivity cut-point used. Several agents have been developed to target MET or HGF. They are divided into small molecule inhibitors and monoclonal

Received: 08.04.2022 Accepted: 08.04.2022 Early publication date: 19.05.2022

antibodies. Currently, two tyrosine kinase inhibitors (TKIs), i.e. tepotinib and capmatinib, have been approved by the Food and Drug Administration (FDA) for the treatment of NSCLC patients with a splice site mutation in exon 14 of the *MET* gene. Response to therapy occurs in 46–68% of patients, depending on the mutation testing method (liquid biopsy *vs.* tissue) and the treatment line. However, it has also been shown that MET inhibitors (crizotinib, cabozantinib, and capmatinib) may be effective in NSCLC patients with *MET* gene amplification [2–5].

Splice site mutations in exon 14 of the *MET* gene are currently examined with the next-generation sequencing (NGS) technique. In turn, with the use of fluorescence *in situ* hybridization (FISH), the ratio of MET to the centromeric portion of chromosome 7 (*CEP7*) can be used to distinguish between chromosome polysomy and gene amplification. However, there are other cheaper, simpler, and faster methods for the examination of *MET* exon 14 mutations and the *MET* gene copy number, e.g. quantitative PCR (qPCR), including one using reverse transcription (RT-qPCR). However, PCR-based methods have numerous limitations, for example, low sensitivity and specificity. In this study, we attempted to detect selected abnormalities in the *MET* gene using various molecular techniques.

Material and methods

Patients

The study group consisted of 26 patients with lung adenocarcinoma (median age: 67.2 ± 8.5 years, 8 women, 18 men) diagnosed and treated in the Department of Pneumonology, Oncology, and Allergology from 2014 to 2019. All enrolled patients had a diagnosis of abnormalities in the *EGFR* gene (real-time PCR method), the *ALK* gene (IHC, FISH, and RT-qPCR methods), the *ROS1* gene (FISH and RT-qPCR methods), the *MET* gene (FISH, qPCR, RT-qPCR methods), and the *RET* gene (qRT-PCR method), as well as assessment of PD-L1 protein expression (IHC method). We enrolled one patient with *ALK* gene rearrangement, one patient with *RET* gene rearrangement, and 6 patients with *EGFR* gene mutations (three with deletions in exon 19 and three with substitution Leu858Arg). Seven patients had PD-L1 expression on ≥ 50% of tumor cells. The *ALK*-positive patient was treated with crizotinib in first-line therapy and alectinib in second-line therapy. Three patients with *EGFR* gene mutations received erlotinib, and other 3 patients with these mutations were administered afatinib. In two patients with progression after erlotinib or afatinib, a Thr790Met mutation was detected and osimertinib was administered. Two *EGFR*-positive patients received chemotherapy with cipslatin and pemetrexed. Only one patient with PD-L1 expression on ≥ 50% of tumor cells was treated with pembrolizumab. The other patients received first-line platinum-based chemotherapy (13 patients — cisplatin plus pemetrexed, 4 patients — cisplatin plus vinorelbine, and one patient — cisplatin plus gemcitabine). In second-line therapy applied in chemotherapy-resistant patients, atezolizumab was used in 9 patients, nivolumab in 2 patients, and docetaxel plus nintedanib in one patient. The median overall survival of our patients was 48 months (95% CI: 16.3–48.0). The demographic and clinical-pathological characteristics of the patients are presented in Table 1.

All aspects of the work covered in this manuscript were approved by the Ethics Committee of the Medical University of Lublin, Poland (No. KE-0254/169/2014).

Table 1. Characteristics of lung adenocarcinoma patients

Characteristics	Number of patients	Percentage of patients
Sex		
Female	8	31
Male	18	69
Stage of disease		
IIIB	8	31
IV	18	69
Smoking status		
Non-smokers	9	35
Former smokers	11	42
Current smokers	6	23
***EGFR* gene mutations**	6	23
Deletion in exon 19	3	11.5
Substitution Leu858Arg	3	11.5
PD-L1 expression on ≥ 50% of tumor cells		
Yes	7	27
No	19	73
First-line treatment	**26**	**100**
Chemotherapy (cisplatin plus pemetrexed or vinorelbine or gemcytabine)	18	69
Pembrolizumab	1	4
Crizotinib	1	4
EGFR TKIs (erlotinib or afatinib)	6	23
Second-line treatment	**17**	**65**
Chemotherapy (cisplatin plus pemetrexed or docetaxel plus nintedanib)	3	12
Immunotherapy (atezolizumab or nivolumab)	11	42
Alectinib	1	4
Osimertinib	2	7

Routine diagnosis of predictive factors in adenocarcinoma patients

DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissues or cytological specimens (cell blocks). DNA was extracted using the QIAamp DNA FFPE Tissue Kit (CE-IVD marked, Qiagen, Germany). Isolation was performed according to the manufacturer's instructions (the same isolated DNA was also used for examination of the *MET* gene copy number using the qPCR technique). The concentration and quality of isolated DNA were estimated by spectrophotometry. Mutations of the *EGFR* gene were identified using the EntroGen *EGFR* Mutations Analysis Kit (CE-IVD marked, EntroGen, Woodland Hills, Canada) in the Cobas Z 480 real-time PCR system (Roche Diagnostics, USA). We examined all the most common mutations in exons 18 to 21 [6].

Abnormal ALK protein and PD-L1 protein expression were examined using an immunohistochemistry test. ALK protein IHC staining was conducted on the Ventana Benchmark GX platform using CE-IVD approved anti-ALK Rabbit Monoclonal Primary Antibody (clone D5F3). The OptiView Amplification Kit and the OptiView DAB IHC Detection Kit were used as detection systems. Rabbit monoclonal negative control immunoglobulin was used as a negative control (Ventana Medical System, Tuscon, USA). CE-IVD approved Ventana SP263 antibody was used for PD-L1 protein IHC staining. The same equipment and detection systems were used for the examination of ALK expression. Rabbit monoclonal negative control immunoglobulin (Ventana Medical System, Tucson, AZ, USA) was used as a negative control. The slides were assessed by pathologists using an Olympus BX41 microscope [7–8].

All positive results of ALK expression obtained in IHC staining were re-evaluated with the FISH method to visualize the presence of *ALK* rearrangement using the Vysis *ALK* Break Apart FISH Probe Kit (Abbot Molecular, USA) and the paraffin-pretreatment IV and Post-Hybridization Wash Buffer Kit (Abbot Molecular, USA). In the diagnosis of *ROS1* gene rearrangement, we used the ZytoLight SPEC ROS1 DualColor Break Apart Probe (ZytoVision, Germany) and the Vysis Paraffin Pretreatment and Post-hybridization Wash Buffer Kit (Abbott, USA). Fluorescence signals were assessed using an Axio Scope microscope (Zeiss, Germany). Interpretation of FISH results was conducted in accordance with the American Food and Drug Administration (FDA) and International Association for the Study of Lung Cancer (IASLC) guidelines [8].

Reverse transcriptase PCR analysis of *ALK*, *ROS1*, and *RET* gene rearrangements and *MET* gene skipping mutations

Total RNA was extracted from FFPE tissues with the miRNeasy FFPE Kit (Qiagen Inc., Germany) according to the manufacturer's instructions. The RNA concentration was measured with Qubit 4 fluorometers (Invitrogen, Thermo Fisher Scientific, Waltham, USA). RNA samples were stored at –80°C until RT-qPCR (reverse transcriptase-quantitative PCR) was performed. The same isolated RNA was also used for the examination of the *MET* mRNA expression.

To detect *ALK*, *ROS1*, and *RET* gene fusions, as well as *MET* exon 14 skipping mutations, we used the Lung Cancer RNA Panel kit (EntroGen, Woodland Hills, Canada) according to the manufacturer's instructions. There were 8 reactions of twenty microliters in the volume of one-step RT-qPCR for one patient. Every reaction mixture contained 10 μL of One-Step RT-qPCR Reaction Mix, 1 μL of RT Enzyme Mix, 4 μL of Reaction Detection Primer Mix (one from eight), and 5 μL of RNA (concentration 16 ng/μL). The RT-qPCR reaction was performed on the Illumina Eco real-time PCR platform (Illumina, San Diego, USA) in the following conditions: 55°C for 10 minutes, 95°C for 1 minute, and next 40 cycles: 95°C for 10 seconds and 60°C for 45 seconds. Ct values were obtained, and analysis was performed according to the manufacturer's instructions.

MET gene amplification assessment with the FISH technique

The *MET* gene amplification status was assessed using the ZytoLight SPEC MET/CEN 7 Dual Color Probe (CE, ZytoLight, Germany). The Paraffin-Pretreatment and Post-Hybridization Wash Buffer Kit (Abbot Molecular, USA) was also used for the pre-staining procedure. Three to five μm thick paraffin sections were cut and mounted on the positively charged glass slides. All procedures were carried out according to the manufacturer's procedure.

The SPEC MET/CEN 7 Dual Color Probe is a combination of a probe with an orange fluorochrome direct labeled specific for the alpha satellite centromeric region of chromosome 7 (D7Z1) and a probe with a green fluorochrome direct labeled targeted at the *locus* in the *MET* gene located at 7q31.2. In a normal interphase nucleus, two orange and two green signals are expected. In cells with amplification of the *MET* gene *locus*, multiple copies of the green signal or green signal clusters will be observed. The fluorescence signals were assessed using an Axio Scope microscope (Zeiss, Germany).

We classified the cases into two categories: *MET*-positive (with amplification) and *MET*-negative (without amplification). The cutoff of the *MET*/*CEP7* ratio was 2.0. A sample was considered to have *MET* amplification if the mean *MET*/*CEP7* ratio was ≥ 2.0 or if the *MET*/CEP7 ratio was < 2.0, but the *MET*-copy number was ≥ 5 copies per nucleus or *MET* signal clusters were seen in more than 10% of tumor cell nuclei. According to a different classification, *MET* amplification was also classified using the low ratio (≥ 1.8 to ≤ 2.2 *MET*/*CEP7*), intermediate ratio (> 2.2 to < 5 *MET*/*CEP7*), and high ratio (≥ 5 *MET*/*CEP7*) [9–10].

MET gene copy number assessment with the qPCR technique

The *MET* gene copy number was assessed using a TaqMan primer set and probe (TaqMan Copy Number Assays, Hs00305306_cn, Thermo Fisher Scientific, Waltham, Massachusetts, USA). RNazeP (TaqMan Copy Number Reference Assay, human, RNaseP, Thermo Fisher Scientific, Waltham, Massachusetts, USA) was used as an internal control. The 10-microlitre qPCR reaction mixture contained 5 μL of Genotyping Master Mix, 0.5 μL of TaqMan Copy Number Assays or TaqMan Copy Number Reference Assay, and 4.5 μL of DNA (concentration 5 ng/μL). The real-time PCR was performed in Illumina Eco (Illumina Inc., San Diego, California, USA). The temperature conditions of qPCR were as follows: enzyme activation at 95°C for 10 minutes followed by 40 cycles of two-stage PCR at 95°C for 15 seconds and next at 62°C for 90 seconds. Method $2^{-\Delta\delta Ct}$ was used for the calculations. The calibrator, which was a mixture of DNA obtained from lymphocytes of healthy subjects, was used for the calculations. According to the literature data, we assumed that more than 3 copies of the *MET* gene allowed us to find a high copy number of this gene.

MET mRNA expression analysis using RT-qPCR

RNA reverse transcription was performed using the High Capacity cDNA Reverse Transcription Kits (Thermo Fisher Scientific, Waltham, Massachusetts, USA) according to the manufacturer's instructions. cDNA was stored at –20° C until qPCR was performed.

The expression of *MET* mRNA (cDNA) was assessed using primers and the TaqMan probe kit (TaqMan™ Gene Expression Assay Hs01565584_m1, Thermo Fisher Scientific, Waltham, Massachusetts, USA). GAPDH (Gene Expression Reference Assay Hs03929097_g1, Thermo Fisher Scientific, Waltham, Massachusetts, USA) was used as an internal control. The composition of the reaction mixture (10 μL) was as follows: 5 μL of TaqMan Fast Advanced Master Mix (Thermo Fisher Scientific, Waltham, Massachusetts, USA), 0.5 μL of TaqMan Gene Expression Assay or GAPDH reference assay, 3.5 μL of nuclease-free water, and 1 μL of cDNA (RT-PCR reaction product). The real-time PCR was performed in Illumina Eco (Illumina Inc., San Diego, California, USA). The temperature conditions of the qPCR reaction were as follows: 50°C for 2 minutes (UNG, uracil-N-glycosylase activation), 95°C for 20 minutes (polymerase activation) followed by 40 cycles of two-stage PCR (95°C for 3 seconds then 62°C for 45 seconds). Method $2^{-\Delta Ct}$ was used for the calculations.

Statistical analysis

The U-Mann Whitney test was used for testing the equality of population medians among groups differing in clinical and demographic factors. The Spearman test was used to calculate the correlation between countable variables. Data were expressed as a percentage (for the categorized variable), median, and standard deviation (for continuous variables). These tests were performed with Statistica v. 13.1 (Tibco Software, USA). Survival analyses were performed using the Kaplan-Meier estimation method in MedCalc 15.8 (MedCalc Software, Ostend, Belgium) with a calculation of the 95% confidence interval (CI). We considered p values below 0.05 to be statistically significant.

Results

In our patients, we did not find *MET* exon 14 skipping mutations with the use of the RT-qPCR technique. We also did not demonstrate the presence of *MET* gene amplification or chromosome 7 polysomy with the FISH technique. The median *MET*/*CEP7* ratio was 1.04 with a standard deviation of 0.145, and the median number of chromosome 7 was 2.5 ± 0,788. In the FISH method, the median *MET* gene copy number was 2.6 ± 0.457. In contrast, the median *MET* gene copy number was 3.43 ± 1.539 in the qPCR study. Fifteen patients had more than 3 copies of the *MET* gene detected by the qPCR technique. According to the criteria adopted by other authors, we may conclude that 57.7% of the patients had a high *MET* gene copy number. The relative *MET* mRNA expression was low, and its median was 0.01 with a standard deviation of 0.045.

The age (division into two groups according to the median), stage of disease (IIIB versus IV), and smoking status did not affect the assessed parameters (*MET*/*CEP7* ratio, *CEP7* number, *MET* gene copy number in the FISH, and qPCR methods, and *MET* mRNA expression). However, the *MET*/*CEP7* ratio and *MET* mRNA expression were slightly higher in

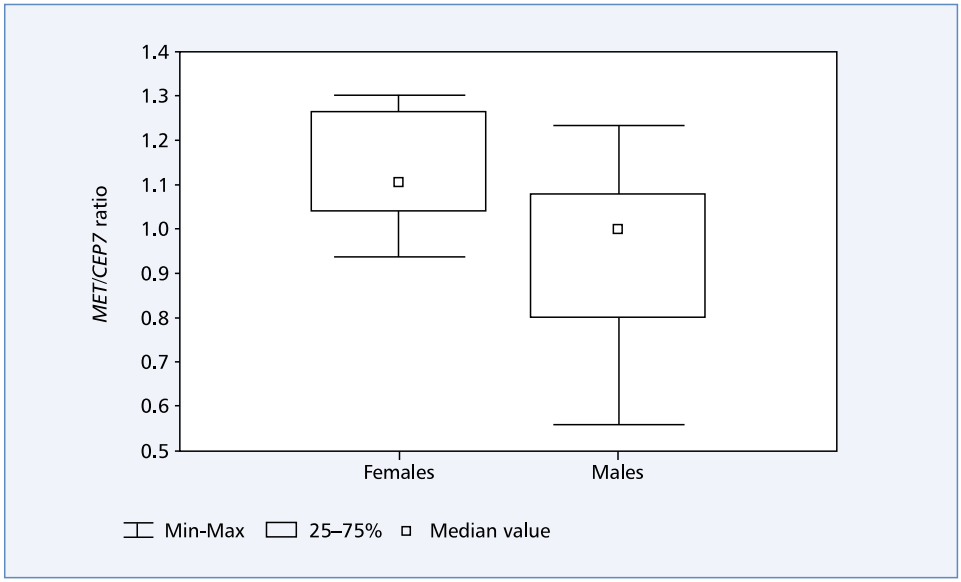

Figure 1. Value of the *MET/CEP7* ratio assessed with the FISH technique depending on the sex of the studied lung adenocarcinoma patients

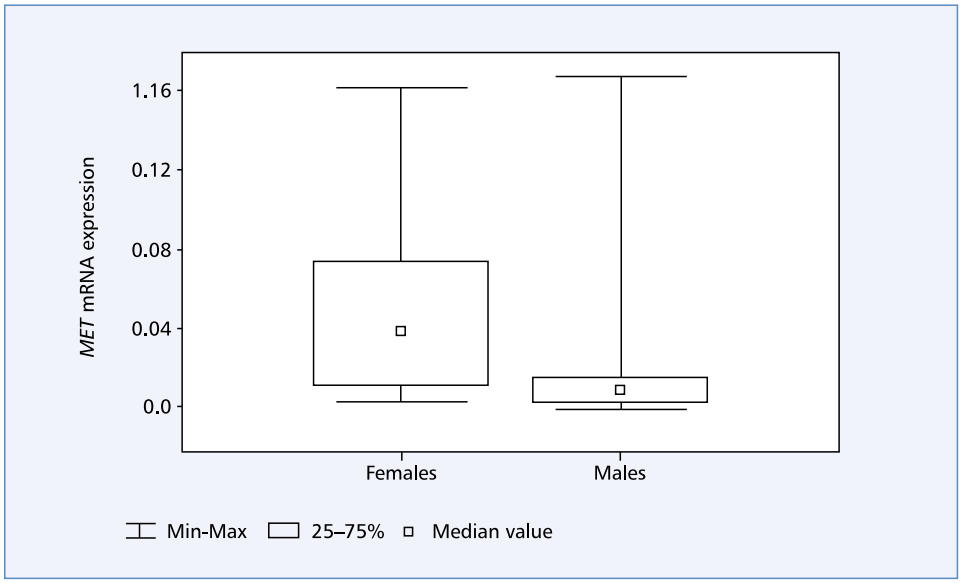

Figure 2. Relative *MET* mRNA expression assessed with the RT-qPCR method depending on the sex of the studied lung adenocarcinoma patients

the women than in the men ($p = 0.054$ and $p = 0.055$, respectively, Fig. 1 and 2). Moreover, the *MET* gene copy number in the FISH method was insignificantly higher in patients with genetic driver alterations (*EGFR* gene mutations, *ALK* and *RET* gene rearrangements) than in patients without these abnormalities ($p = 0.077$, Fig. 3).

We found a significant positive correlation ($R = +0.573$, $p = 0.0022$) between the *MET* gene copy number assessed with the qPCR method and the relative *MET* mRNA expression (Fig. 4). We did not detect a correlation between the *MET/CEP7* ratio and the *MET* gene copy number assessed with the qPCR method, as well as the *MET* mRNA expression. The *MET* gene copy number in the FISH technique did not significantly correlate with the *MET* gene copy number assessed with the qPCR technique and with the relative *MET* mRNA expression.

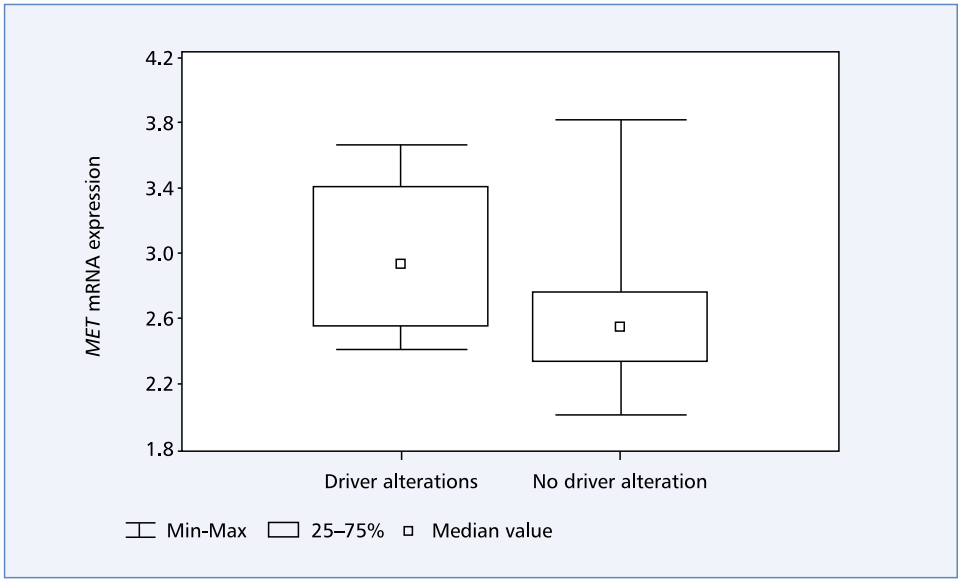

Figure 3. *MET* gene copy number assessed with the FISH method in patients with and without genetic driver alterations (*EGFR* gene mutations, *ALK* and *RET* gene rearrangements)

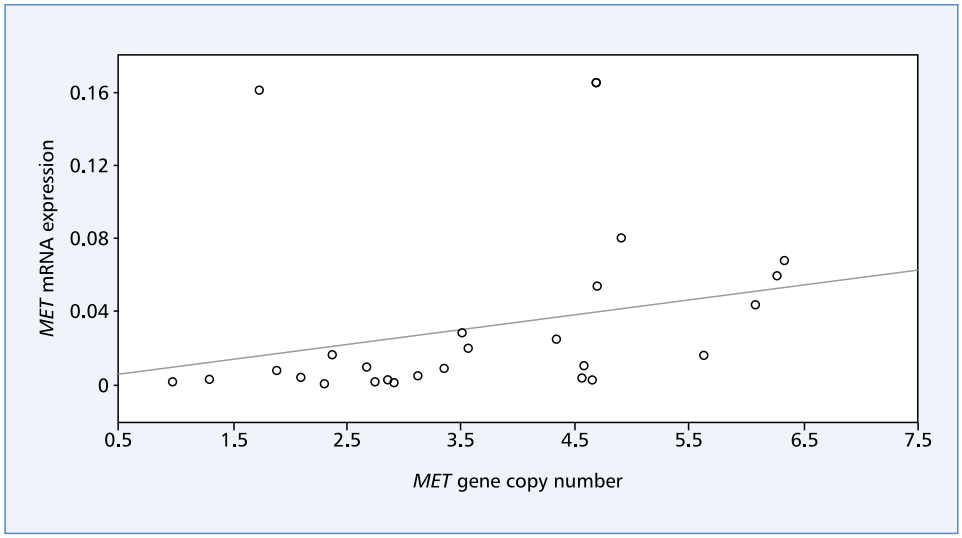

Figure 4. Significant positive correlation between the *MET* gene copy number assessed with the qPCR method and the relative *MET* mRNA expression in lung adenocarcinoma patients

Discussion

Most studies on the CNV of *MET* gene have been conducted in Asian populations. However, two studies on Caucasian NSCLC patients need to be mentioned. Capuzzo et al. [9], studied the CNV of the *MET* gene using the FISH technique in 435 Italian NSCLC patients, and Bubendorf et al. [11] studied abnormalities in the *MET* gene using the silver in situ hybridization (SISH) technique in the European population. Capuzzo et al. were the first to introduce a *MET* gene amplification evaluation system using the FISH technique. They found a high *MET* gene copy number (mean ≥ 5 copies/cell) in 48 cases (11.1%), including 18 cases with true gene amplification (4.1%). The high *MET* gene copy number was associated with an advanced stage ($p = 0.01$), a low grade of tumor differentiation ($p = 0.016$), and amplification of the *EGFR* gene in tumor cells ($p < 0.0001$). The authors found no relationship between patients' sex and the *MET* gene copy number in the cancer cells. No patient with an *EGFR* activating mutation showed a high *MET* gene copy number. *MET*-positive patients had

shorter survival than *MET*-negative patients (p = 0.005) [9]. These results differ from those presented in our study in which we showed that the women and patients with genetic driver alterations had a slightly higher *MET* gene copy number than the men and patients without other genetic abnormalities. On the other hand, we did not find patients with true *MET* gene amplification with an oncogenic character (responsible for tumor growth). This is likely to be related to the high percentage of patients with other genetic driver alterations included in our study. Driver abnormalities do not usually coexist in one patient.

Bubendorf et al. published results from the European Thoracic Oncology Platform (ETOP) Lungscape Project, which involved 1572 patients with surgically resected NSCLC. *MET* gene amplification was defined as a *MET*/*CEP7* ratio ≥ 2 and a high *MET* gene copy number as ≥ 5, as well as high MET protein expression in the IHC test as ≥ 2 + intensity in ≥ 50% of tumor cells. One hundred and eighty-two patients with MET protein expression and without mutations in the *EGFR* and *KRAS* genes were analyzed for the *MET* exon 14 skipping mutation. The high expression of the MET protein was significantly associated with the female sex and small tumor size. *MET* amplification occurred in 4.6% of patients, and a high *MET* gene copy number was detected in 4.1% of patients. The *MET* gene abnormalities were not significantly associated with the clinical and demographic characteristics of the patients. The *MET* exon 14 skipping mutation was detected in 5 of the 182 (2.7%) patients, including 4 adenocarcinoma patients (4.5%). The authors emphasized that the large inter-laboratory variability in the *MET* status assessment highlights the challenge of these analyses in routine practice [11].

Dziadziuszko R et al. [12] assessed the *MET* gene copy number using the SISH technique in 140 Polish NSCLC patients. The median value of the *MET* gene copy number per cell was 3.12 (from 1.74 to 11.84). Three patients (2.1%) showed gene amplification (*MET* gene clusters) and 14 (10%) had tumors with 5 or more gene copies per nucleus. There was a significant correlation between the *MET* copy number and the protein expression. The authors found no association between the *MET* gene copy number and the demographic or clinical features, including sex (p = 0.54), disease stage (p = 0.21), tumor grade (p = 0.86), and histology (p = 0.84), or smoking status (p = 0.47). They showed no associations between the *MET* copy number and disease-free survival or overall survival. In our study, we found that the median *MET* gene copy number tested with the qPCR technique exceeded 3, which is consistent with the observations reported by Dziadziuszko et al. [12], who used the FISH technique. It is debatable whether 3 or more copies of the gene should be used as a cutoff point for recognition of a high *MET* gene copy number in NSCLC patients [12].

In another study on the Polish NSCLC population, Kowalczuk et al. [13] used the qPCR technique to study the *MET* gene copy number and mRNA *MET* expression. In total, 151 patients with paired surgical samples of tumor and tumor-distant normal lung tissues were enrolled in the study. A high *MET* gene copy number (more than 3.0 copies per cell) was found in 18.5% of patients and occurred more frequently in adenocarcinoma with an increased *EGFR* and *HER2* gene copy number and with *EGFR* activating mutations (p = 0.051). The *MET* mRNA expression was 1.76-fold higher in the tumor compared to unaffected lung tissue, and it was associated significantly with the *MET* gene copy number. The results of this study are partially consistent with our results [13].

Aguado et al. [14] examined 422 NSCLC patients and identified 13 patients (3%) with *MET* exon 14 mutations and 15 patients (3.5%) with very high *MET* mRNA expression, which was analyzed using the quantitative transcript-based hybridization technology. These two subgroups of patients were mutually exclusive, displayed distinct phenotypes, and did not generally coexist with other genetic driver alterations. Ninety-two percent of patients with very high *MET* mRNA expression had *MET* gene amplification detected by FISH and/or NGS. However, FISH failed to identify three patients with very high *MET* mRNA expression, among whom one received MET tyrosine kinase inhibitors and obtained clinical benefit. These results indicated that *MET* mRNA expression assessment could improve the selection of patients for MET TKIs [14].

Kim JH et al. [15] performed a meta-analysis to evaluate the prognostic value of a high *MET* gene copy number in NSCLC patients. From 21 studies, 7647 patients were included in the pooled analysis of hazard ratios for disease-free survival or overall survival. Patients with a high *MET* gene copy number showed significantly worse survival than patients with a low *MET* gene copy number. The method used for *MET* CNV analysis included FISH, SISH, bright field in situ hybridization (BISH), and qPCR. The FISH technique was mostly used, but various cutoff criteria were adopted. A high *MET* gene copy number occurred in 1–38.9% of patients, depending on the technique used and the cut-point for positivity. Using the qPCR technique, more than 3 *MET* gene copies were considered a high *MET* gene copy number in most studies. A high *MET* gene copy number was detected in 5.6%, 18%, and 18.5% of NSCLC patients. In one study, the cutoff was the mean *MET* gene copy number, which was 1.31. In this study, a high *MET* gene copy number was found in 4.8% of patients. Surprisingly, there is a large discrepancy in the results and the fact that as many as 57.7% of patients

in our study had over 3 *MET* gene copies detected by the qPCR test [15].

Conclusions

Our study has several inherent limitations that need to be discussed. The group of adenocarcinoma patients was very small. Moreover, the group was heterogeneous regarding the occurrence of somatic driver alterations. Therefore, we did not detect any rare abnormalities in the *MET* gene. The 3 gene copy number cutoff for our qPCR test appears to be understated. This produces incorrect high *MET* gene copy number results in several patients. Nevertheless, the agreement of the *MET* mRNA expression and FISH results, as well as the positive correlation between the *MET* mRNA expression and the *MET* gene copy number in the qPCT test, indicate that these methods could complement each other. Performance of these two tests simultaneously (e.g. determination of mRNA expression and gene copy number) increases the reliability of *MET* gene assessment. Such a tool allows correct qualification of our patients for molecularly targeted therapies.

Conflict of interest

Authors declare no conflict of interest.

References

1. Organ SL, Tsao MS. An overview of the c-MET signaling pathway. Ther Adv Med Oncol. 2011; 3(1 Suppl): S7–SS19, doi: 10.1177/1758834011422556, indexed in Pubmed: 22128289.
2. AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine through an International Consortium. Cancer Discov. 2017; 7(8): 818–831, doi: 10.1158/2159-8290.CD-17-0151, indexed in Pubmed: 28572459.
3. Drilon A, Cappuzzo F, Ou SHI, et al. Targeting MET in Lung Cancer: Will Expectations Finally Be MET? J Thorac Oncol. 2017; 12(1): 15–26, doi: 10.1016/j.jtho.2016.10.014, indexed in Pubmed: 27794501.
4. Paik PK, Felip E, Veillon R, et al. Tepotinib in Non-Small-Cell Lung Cancer with Exon 14 Skipping Mutations. N Engl J Med. 2020; 383(10): 931–943, doi: 10.1056/NEJMoa2004407, indexed in Pubmed: 32469185.
5. Wolf J, Seto T, Han JY, et al. GEOMETRY mono-1 Investigators. Capmatinib in Exon 14-Mutated or -Amplified Non-Small-Cell Lung Cancer. N Engl J Med. 2020; 383(10): 944–957, doi: 10.1056/NEJMoa2002787, indexed in Pubmed: 32877583.
6. Mok T, Carbone D, Hirsch F. IASLC atlas of EGFR testing in lung cancer. 2017. https://www.iaslc.org/research-education/publications-resources-guidelines/iaslc-atlas-egfr-testing-lung-cancer-guidebook.
7. Tsao MS, Kerr KM, Dacic S et al. The IASLC Atlas of PD-L1 Testing in Lung Cancer. 2017. https://www.iaslc.org/research-education/publications-resources-guidelines/iaslc-atlas-pd-l1-testing-lung-cancer.
8. Tsao MS, Hirsch FR, Yatabe Y. IASLC atlas of ALK and ROS1 testing in lung cancer. 2016. https://www.iaslc.org/research-education/publications-resources-guidelines/iaslc-atlas-alk-and-ros1-testing-lung-cancer.
9. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. J Clin Oncol. 2009; 27(10): 1667–1674, doi: 10.1200/JCO.2008.19.1635, indexed in Pubmed: 19255323.
10. de Melo Gagliato D, Jardim DL, Falchook G, et al. Analysis of MET genetic aberrations in patients with breast cancer at MD Anderson Phase I unit. Clin Breast Cancer. 2014; 14(6): 468–474, doi: 10.1016/j.clbc.2014.06.001, indexed in Pubmed: 25065564.
11. Kerr KM, Dafni U, Schulze K, et al. ETOP Lungscape Consortium, Lungscape Consortium. Prevalence and clinical association of MET gene overexpression and amplification in patients with NSCLC: Results from the European Thoracic Oncology Platform (ETOP) Lungscape project. Lung Cancer. 2017; 111(1): 143–149, doi: 10.1016/j.lungcan.2017.07.021, indexed in Pubmed: 28838386.
12. Dziadziuszko R, Wynes MW, Singh S, et al. Correlation between MET gene copy number by silver in situ hybridization and protein expression by immunohistochemistry in non-small cell lung cancer. J Thorac Oncol. 2012; 7(2): 340–347, doi: 10.1097/JTO.0b013e318240ca0d, indexed in Pubmed: 22237262.
13. Kowalczuk O, Kozlowski M, Niklinska W, et al. Increased MET Gene Copy Number but Not mRNA Level Predicts Postoperative Recurrence in Patients with Non-Small Cell Lung Cancer. Transl Oncol. 2014; 7(5): 605–612, doi: 10.1016/j.tranon.2014.08.002, indexed in Pubmed: 25389455.
14. Aguado C, Teixido C, Román R, et al. Multiplex RNA-based detection of clinically relevant MET alterations in advanced non-small cell lung cancer. Mol Oncol. 2021; 15(2): 350–363, doi: 10.1002/1878-0261.12861, indexed in Pubmed: 33236532.
15. Kim JH, Kim HSu, Kim BJ. Prognostic value of MET copy number gain in non-small-cell lung cancer: an updated meta-analysis. J Cancer. 2018; 9(10): 1836–1845, doi: 10.7150/jca.24980, indexed in Pubmed: 29805710.

VIA MEDICA

REVIEW ARTICLE

Catarina Rodrigues[1, 2], Bárbara Gomes[3, 4], Carlos Albuquerque[5, 6]

[1]ICBAS School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal
[2]Department of Oncology, CHTMAD, EPE, Vila Real, Portugal
[3]Porto Higher School of Nursing, Porto, Portugal
[4]UNIESEP/CINTESIS
[5]Higher School of Health/Polytechnic Institute of Viseu, Viseu, Portugal
[6]UICISA

The rehabilitation of cancer patients and the role of nurses: a scoping review

Address for correspondence:
PhD student in Nursing Sciences
or Master Degree (MS), Rehabilitation
Nurse Catarina Rodrigues
Department of Oncology,
Centro Hospitalar de Trás-os-Montese
Alto Douro, EPE, Av. da Noruega, Lordelo,
5000–508 Vila Real. Portugal
e-mail: acataryn@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0018

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Cancer survivors represent a growing population with very specific physical and psychosocial needs. The nurse's intervention is focused on the management of symptom burden and challenges due to cancer, treatment-related morbidities, the maximization of independence, and the improvement of the quality of life of cancer patients. The purpose of this scoping review is to identify different specific rehabilitation interventions delivered by nurses in response to physical, psychological, and cognitive impairments that may be experienced by cancer patients and to understand whether these interventions should be implemented at a specific phase of cancer care.

Methods. A scoping review was performed (Joanna Briggs Institute, 2019) and multiple databases and Google Scholar were searched from January 2016 to August 2021. Articles published in English, Spanish or Portuguese, which included nurses who provided evidence-based rehabilitation interventions and psychosocial support, patient education, and health promotion to adult cancer patients, were considered for inclusion.

Results. A total of 59 studies were included yielding 3 nurse-led intervention categories: exercise, psychoeducation, complementary and alternative medicine therapies. Most nurse-led interventions were delivered after cancer surgery or during treatment. Outcomes were mostly symptom-focused and frequently included quality of life. Many interventions provided beneficial physical and psychological outcomes or showed a positive trend.

Conclusions. Scientific publications concerning nurses as cancer rehabilitation providers still come as a relatively new approach. Further research and tailored interventions are needed to help nurses in decision-making and evidence-based practice.

Key words: cancer rehabilitation; rehabilitation nursing; oncology nursing; exercise therapy; psychological techniques; complementary therapies

Oncol Clin Pract 2022; 18, 3: 147–165

Introduction

Today, cancer is a major public health problem [1] and the second leading cause of death worldwide, following cardiovascular diseases [2]. The number of new cases is expected to rise from 14 million to 22 million by 2030; this is about a 70% increase in only two decades [3]. Nevertheless, the advances made in early diagnosis and medical and surgical care, such as targeted therapies and new exacting procedures, have led to increased life expectancy following cancer [2].

Received: 28.02.2022 Accepted: 22.03.2022 Early publication date: 19.05.2022

Cancer treatment requires careful consideration of evidence-based options, which can include more than one of the most common therapeutic modalities, such as surgery, radiotherapy, and systemic therapy [4]. While lifesaving, these interventions are often inevitably aggressive and invasive, triggering a variety of symptoms that can limit patients' function and participation [5, 6], and significantly impact health-related quality of life (QoL). These morbidities may become evident in a pre-diagnostic stage or through many years after cancer treatment, leading to the necessity for further complex physical and psychological demanding treatments [6]. Several treatment-related morbidities or symptoms are amenable to rehabilitation interventions, such as fatigue, cognitive impairment, pain, sexual disfunction, balance and gait problems, lymphedema, swallowing, and communication difficulties, among others [7]. The variety of symptoms that can be addressed may be the reason behind the growing interest in this area.

Rehabilitation is considered an essential health service focused on the functioning of individuals with a variety of health conditions, not only in disease, but during all phases of life-course, and throughout all stages of acute, sub-acute, and long-term care [4]. Targeted rehabilitation interventions may decrease the incidence and/or the severity of upcoming impairments, which leads to reduced surgical complications and diminished hospitalizations or readmissions [6]. Furthermore, cancer rehabilitation is a multidisciplinary and multimodal approach that provides assessment, treatment, and support focusing on individuals' needs, which consequently has the ability to improve physical and psychological health outcomes. This enhancement is obtained by reducing disability and by improving the patient's capacity to fully participate in work activities and enjoy leisure time, substantially increasing their QoL [4, 6–8].

Despite all these benefits, nowadays most delivery models of care do not integrate comprehensive cancer rehabilitation services into the oncology care continuum [8, 9], and when present, rehabilitation services are significantly underused in all phases of cancer care [7].

A cancer rehabilitation team comprises interdisciplinary providers that must work together to design tailored interventions, with the intention of restoring function, enhancing participation, and/or preventing a later effect of the treatments [7]. This multidisciplinary approach to quality care for cancer survivors requires competency in assessment, decision-making, coordination, and communication skills, indispensable in every discipline, including nursing [9].

The theoretical framework for this review incorporates elements of Orem's Self-care deficit nursing theory [10], which is based on the assumption that people with knowledge and information are enabled to participate in self-care activities that facilitate the management of physical and psychological problems, leading to the improvement of their health results. Orem's theory is composed of three interconnected theories: (1) the theory of self-care, (2) the self-care deficit theory, and (3) the theory of nursing systems. The Nursing Process presents a system that helps determine self-care deficits at any stage of the patient's life and aids to define their roles and the role of nurses involved in meeting self-care demands, whether in the maintenance of well-being, recuperation of health, prevention of illness, or rehabilitation [10].

Scientific publications in cancer rehabilitation are growing at a faster rate, but the field of nurse-led interventions is still relatively new, and the literature has not yet been sufficiently synthesized to assist health professionals and researchers in decision-making and to provide the best evidence-based practice. We conducted a preliminary electronic search for existing scoping or systematic reviews on the subject in the JBI Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, CINAHL®, and PubMed®, up to August 2021. The existent summarized evidence regarding nurse-led rehabilitation programs, normally only approaches a specific phase of the cancer care continuum (e.g., post-operative period or palliative phase).

The objective of this review is to map the available evidence that identifies different rehabilitation interventions delivered by nurses in response to physical, psychological, and cognitive impairments that may be experienced by cancer patients and to understand whether these interventions should be implemented at a specific phase of cancer care.

Methods

The guidelines of the Joanna Briggs Institute Reviewer's Manual [11] were followed to conduct this scoping review. The final report should comprise different components and, following this process, a pertinent review question was identified:

"What specific nurse-led rehabilitation care is provided to cancer patients?"

Inclusion criteria

This review considered studies including nurses who specialize in oncology or rehabilitation nursing or provided evidence-based rehabilitation interventions and psychosocial support, patient/family education, care coordination, and health promotion to adult cancer patients, regardless of diagnosis and across the continuum of care. Articles including intervention studies with a nurse as the primary investigator were also considered.

Studies comprising nurse-led interventions with a physical component, a psychosocial component, and/or a complementary and alternative module (e.g., music) were considered. These interventions could be provided individually or in group sessions, in person or via telephone/internet, and in any setting (e.g., hospital, rehabilitation units, home). Eligible studies could comprise control groups, that did not receive a nurse-led intervention or that underwent standard care, rehabilitation programs with different levels of intensity or length, or different delivery settings.

This scoping review included any type of study, especially meta-analyses, systematic or integrative reviews, randomized controlled trials (RCTs) including quasi-RCTs, evidence-based clinical practice guidelines, and observational, descriptive, or qualitative studies.

Search strategy

A comprehensive three-step search strategy was developed to find both published and unpublished primary studies and reviews. First, an initial limited search of PubMed® and CINHAL® was performed, followed by an analysis of words in the title, abstract, and index terms used in articles. A second examination using all identified keywords and index terms was undertaken across all included databases. Thirdly, the reference lists of all reports and articles of the studies that have been included in this review were searched for further studies.

Articles published in English, Spanish or Portuguese were considered for inclusion. Databases were searched from January 2016 to August 2021, due to the scarcity of articles regarding rehabilitation interventions provided by nurses to cancer patients. Databases searched included: PubMed®, CINAHL Complete®, SciELO®, and BVS. The search for grey literature included Google Scholar.

Study selection

All results from the searches were uploaded into a reference manager database (Mendeley®) and duplicates were removed. Titles and abstracts were independently reviewed by two authors and inclusion decisions were made by consensus. The full texts were retrieved and assessed against the inclusion criteria.

Data extraction

The data retrieved from the papers were extracted by two independent reviewers, using an adapted results extraction tool from JBI [11]. The disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer. The study material collected includes standard article information (author, year of publication, country), study design, intervention details, duration of the intervention, target population, sample size, and key findings.

Presentation of results

Data analysis using the data collection instrument provided an overview of the obtained evidence from the conducted research concerning the nurse's intervention in the rehabilitation of cancer patients. Search results and article selection were summarized in a flowchart adapted from the Preferred Reporting Items for Systematic reviews and MetaAnalyses (PRISMA) flowchart developed by Moher et al. [12].

Results were presented in a visual form with tables, and a narrative summary accompanied tabulated results. The quality and risk of bias evaluations were not performed because this study did not aim to provide an answer to a specific issue but to provide an overview of existing rehabilitation interventions.

Results

The databases searches yielded a total of 1125 studies. An additional 3 articles were found through other sources. After duplicates were eliminated (n = 21), the titles and abstracts of 1107 studies were screened and 177 were considered for further detailed evaluation. A total of 118 full-text articles were eliminated as they did not meet the inclusion criteria, yielding a total of 59 studies for inclusion in the review. A flowchart showing the number of studies considered at each stage is presented in detail below (Fig. 1).

Three major nurse-led intervention categories were found after a detailed analysis of the studies included in this review: exercise (n = 31), psychoeducational intervention and/or counseling meetings (n = 22), and complementary and alternative medicine (CAM) therapies (n = 6).

This study presents interventions for the management of cancer-related fatigue (CRF), pain, distress, physical impairment, sexual and cognitive function, QoL, depression, sleep disturbances, and other symptoms and challenges (e.g., work limitations).

As cited previously, the theoretical framework for this scoping review incorporates elements of Orem's Self-care deficit nursing theory [10]. One of the three interconnected concepts is the theory of nursing systems, which is further classified into wholly or partly compensatory or supportive-educative. From the analyses of the studies, it was clear that the role of nurses in cancer rehabilitation is mainly supportive-educative (88.1%) and only 11.9% of the nurse intervention was partially compensatory for self-care deficits.

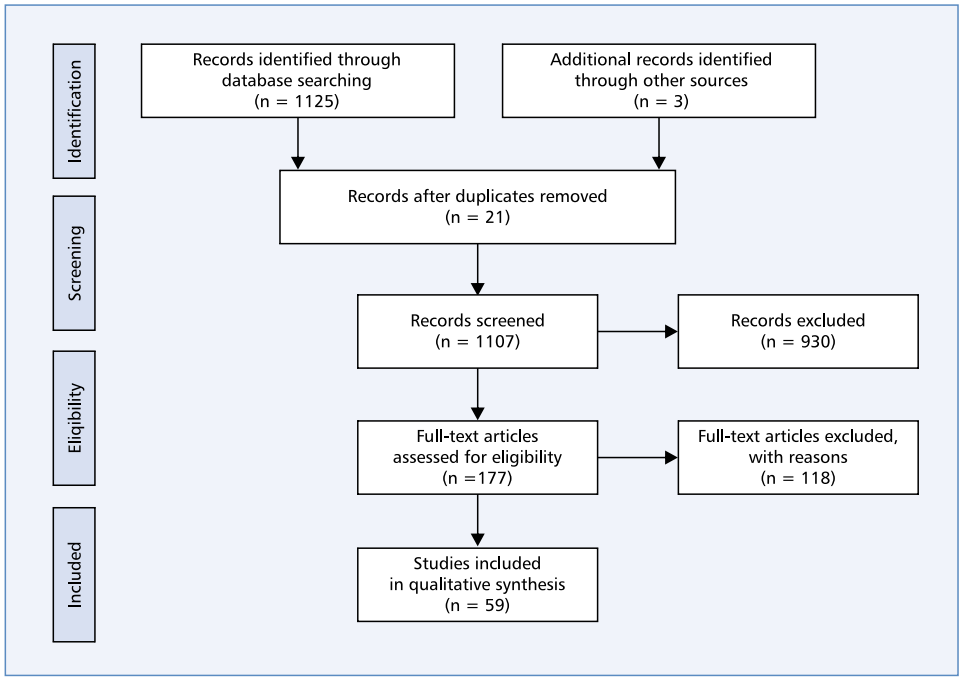

Figure 1. Flowchart of study selection and inclusion process [12]

Most articles were published from 2019 to 2020 (n = 31; 52.5%), and the studies were carried out in the following countries: China (n = 14), the United States of America (USA; n = 11), Turkey (n = 7), Brazil, the United Kingdom, Australia, Iran and Denmark (n = 3), the Netherlands, Sweden, and Taiwan (n = 2).

This scoping review comprises studies with a wide range of study designs: RCT (n = 19); literature, systematic or integrative reviews (n = 15); meta-analysis (n = 7), pre-to-post design (n = 6), qualitative (n = 5), mixed-methods (n = 1), and others.

Most of the articles did not specify cancer location or reported mixed cancer diagnosis (n = 19). However, some studies were conducted only on women with breast cancer (n = 13) or comprised breast cancer among other cancer types (n = 4). The remaining analyzed studies also included the diagnosis of lung cancer (n = 7), gynecological cancer (n = 5), esophageal cancer (n = 3), colorectal, prostate cancer, head and neck cancer (n = 2), lymphoma, leukemia, and high-grade glioma.

All studies were conducted only in adults who were diagnosed with any type and stage of cancer throughout the cancer continuum of care. Nurse-led interventions were delivered after cancer surgery (n = 16), except in two studies, where these interventions were initiated in the pre-operative period. Other research, included cancer patients undergoing active treatment (n = 16), radiation or chemotherapy, or in survivorship (n = 10). Many articles did not specify the phase of cancer treatment (n = 16), and only 1 study was conducted on patients receiving palliative care exclusively.

The outcomes measured across studies included a physical and/or psychosocial component, but the majority were symptom-focused. The number of outcomes evaluated ranged from 1 to 9, with a mean of 3 outcomes per study.

It was found that QoL is one of the most highlighted outcomes assessed either in the overall analysis of studies (35.6%) or in the exercise category specifically. CRF was the most frequently targeted symptom, arising as an outcome assessed in 27.1% of the studies, followed by physical functioning (20.3%) and anxiety (16.9%).

Exercise/physical activity

Exercise interventions delivered by nurses in response to problems that may be experienced by cancer patients have been analyzed in several studies (Tab. 1).

Regarding interventions to improve CRF, al Maqbali et al. [13] conducted a systematic review including 5 studies with gynecologic cancer patients, and the evidence suggests that exercise results in a significant reduction in fatigue despite variations observed between studies (intensity, frequency, duration, and length). The current literature also recommends physical exercise with a multimodal approach, and that includes progressive resistance training with adjustable intensities of aerobic fitness to address CRF [14], leading to an overall improved QoL [15, 16]. A meta-analysis that included 113 RCTs with exercise, psychological, and exercise plus psychological interventions, demonstrated an improvement in CRF during and after primary treatment,

Table 1. Nurse-led exercise interventions

Author and location	Design	Intervention Details	Population	Findings
Huether et al. [16], 2016. USA	Pre-to-post design	Energy Through Motion (ETM): low-to--moderate intensity exercise and/or resistance exercise. Regular personal connections. Follow-up phone calls. Duration: 3 months	50 adults living with/after cancer: UC (n = 30) and EG (n = 20)	ETM participants reported increased activity levels, decreased fatigue and an improved QoL
McGowan [14], 2016 USA	Literature review	Physical exercise to address CRF in inpatient setting, with a variety of intervention dimensions (timing, duration) and exercise dimensions (frequency, intensity, type and time)	Cancer patients	7 articles included. Current literature supports NCCN exercise guidelines, a multimodal approach and progressive resistance training with varying intensities of aerobic fitness
Mustian et al. [17], 2017 USA	Meta-analysis	Exercise (aerobic, anaerobic or strength, or both), psychological (CBT, psychoeducational or eclectic), the combination of exercise and psychological, and pharmaceutical interventions. Mean duration: 14 weeks (range, 1–60)	11 525 unique participants: women with breast cancer (46.9%) and patients with other cancer types	113 RCTs included. Exercise, psychological, and exercise plus psychological interventions improved CRF during and after primary treatment, but pharmaceutical interventions did not
Scott & Posmontier [15], 2017 EUA	Integrative Review	Exercise interventions: aerobic or resistance exercise, cardiovascular exercise, strength training, flexibility exercises, resistive exercise and psychosocial support, walking or a combination of cycling, resistance or strength training, relaxation, basic yoga-type cooldown exercises	Cancer patients under/after treatment	7 studies were selected. Exercise can decrease the effects of CRF, leading to an overall improved QoL. No negative results on the effects of exercise on CRF were reported
McDonald et al. [20], 2018 USA	Pre-to-post design (single-group)	6-week home-based personalized behavioural PA intervention with fitness graded motion exergames (PAfitME): Wii Fit exergames. 1h visit from an oncology nurse and 10-min weekly calls for 3 weeks after the 6-week. Duration: 9 weeks	8 Head and neck cancer patients after cancer treatment	ADL dependence and CRF were significantly reduced. Balance, muscle strength, shoulder forward flexion and cardiorespiratory fitness improved after the 6-week intervention
Sweegers et al. [33], 2018 Netherlands	Systematic Review and Meta-analysis	Exercise, characterized by a variety of intervention dimensions (timing, duration and delivery mode) and exercise dimensions (frequency, intensity, type and time). Duration: from ≤ 12 weeks to > 24 weeks	Adult cancer patients	66 RCTs included. Patients in EG had significantly improved QoL and Physical Function. Significant beneficial effects noted for supervised exercise interventions, but not for unsupervised approaches. Concerning to unsupervised exercise, higher weekly energy expenditure was more effective than lower energy expenditure
Schumacher & McNiel [21], 2018 USA	Exploratory mixed-methods study	Exercise rehabilitation — physical and psychosocial outcomes of the Livestrong at the YMCA program (twice a week, 75 min): cardiovascular conditioning, strength training, balance and flexibility. Face-to-face interviews (35–40 min) Duration: 12 weeks	158 cancer survivors (physical outcomes); 68 participants (psychosocial outcomes); and 11 participants (interviewed about their experience)	Physical measures of strength, balance, flexibility and endurance; and psychosocial measures of anxiety, fatigue, sleep disturbance, satisfaction with social role and pain interference were significantly improved post-exercise rehabilitation

→

Table 1 cont. Nurse-led exercise interventions

Author and location	Design	Intervention Details	Population	Findings
Mendes & Barichello [22], 2019 Brazil	Integrative Review	Non-pharmacological interventions for oncological fatigue and/or HRQOL	Patients with digestive neoplasia undergoing chemotherapy	6 studies were selected. The practice of PA was considered an effective intervention, but no acupuncture, in the management of CRF and HRQOL
al Maqbali et al. [13], 2019 United Kingdom	Systematic review	Exercise interventions to manage CRF, (similarity in the exercise modality), but the intensity, frequency, duration and the length of the exercises varied between studies. PA: 30 min for 5 days (150 min/week). Intervention starts with a counselling session, but the contact with participants is variable. Duration: from 24 weeks to 12 months	Women with gynaecologic cancer	5 studies met the inclusion criteria: 3 RCT and 2 single-arm trials. Evidence suggest that exercise interventions result in significant reductions in fatigue, but, the current evidence is limited
Mardani et al. [27], 2021 Iran	RCT	Exercise booklet and an Exercise programme: aerobic (walking, reached 150 min/week in the last 4 weeks), resistant (11 exercises for large muscles, gradually reached 12 times in 2 sets in the last 2 weeks), flexible (10 exercises for the elongation of main muscles and tendons) and pelvic floor muscle exercises. One session of group exercise and three sessions of individual exercise per week. Duration: 12 weeks	80 Prostate cancer survivors: CG (n = 40) and EG (n = 40)	In the EG statistically significant improvements in physical, role, emotional, social and sexual function were reported. In addition, this group reported reduced fatigue, insomnia, constipation, diarrhea, and other treatment-related symptoms. in comparison with before the exercise program
Groen et al. [34], 2018 Canada	Systematic Review and Meta-analysis	PA interventions (no more than one face-to-face contact): print material, print and telephone or text and telephone, telephone support, web/online support, mobile app, smartphone, text messaging, telemedicine, Nintendo Wii Fit, DVD. Mean duration 3.5 months (range, 1–24)	5 218 Cancer survivors: breast cancer survivors (45%) and other cancer types survivors	29 RCTs included. Moderate-to-vigorous physical activity data from 24 RCTs were included in the meta-analysis and showed an overall small effect, as for steps, supporting the interventions. Three of these studies used telephone calls and the adherence was very high
Zhou et al. [40], 2020 China	RCT	WeChat-based multimodal nursing program: physical (e.g., tailored information, surgical side upper limb exercise training, coping with fatigue and poor sleep, pain relieving), psychological (e.g., relaxation training, feeling expression, counselling) and social rehabilitation (e.g., adaptation to patient role, social training, role transformation). Duration: 6 months	Postoperative women with breast cancer (stage I-III): EG (n = 56) and CG (n = 55).	Significant improvement in the QoL in the EG during early rehabilitation. Physical well-being only exhibited a time-based effect; social/family well-being and functional well-being had group, time, and group-time interaction effects; emotional well-being had time and group-time interaction effects
Chang et al. [39], 2020 Taiwan	RCT	Informatics-based exercise and health information program: a home-based walking exercise program (3-5 days per week for 30 min), a nursing education program (e-books for diet guidance, rehabilitation exercises, symptom management and psychological adjustments), and instruction in use of the health informatic system Duration: 12 weeks	88 Patients who had undergone an esophagectomy for cancer: EG (n = 44) and CG (n = 44).	EG experienced significant improvements in nutrition, exercise capacity and variables related to QoL

→

Table 1 cont. Nurse-led exercise interventions

Author and location	Design	Intervention Details	Population	Findings
Frensham et al. [37], 2020 Australia	Quasi-RCT	Walking intervention (online): the STRIDE website and weekly step goals. All participants attended 2 baselines workshops and were provided with a sealed pedometer and with lifestyle information. The EG was instructed on how to use the website, including how to log steps and report ratings of perceived exertion and daily affect. Duration: 12 weeks	91 Cancer survivors: EG (n = 46) and CG (n = 45)	An increase in steps/day at 12weeks was observed in both groups, with a larger increase in the EG, but changes were not maintained at follow-up. Psychological predictors of maintained changes in steps per day did not differ between metropolitan and rural participants.
Sotirova et al. [35], 2021 United Kingdom	Systematic review and narrative synthesis	Internet-based self-management programmes for post-surgical cancer rehabilitation: an exercise or PA-based self-management intervention and a measure of adherence, acceptability or user satisfaction.	Adult participants after cancer surgery	11 papers included. Interventions had wide variations regarding the adherence levels. Increased acceptability and user satisfaction were linked to interventions which were seen as time and cost-efficient. The majority contained behaviour change components.
Hoffman & Brintnall [36], 2017 USA	Qualitative study	6-week home-based exercise intervention: self-management of CRF (virtual reality using the Nintendo Wii Fit Plus; face-to-face contact followed up with phone contact; use of informational motivators)	37 Non-small cell lung cancer (NSCLC) patients after thoracotomy	Postsurgical NSCLC participants found this rehabilitative exercise intervention acceptable because it removed traditional barriers to exercise
Nemli [38], 2018 Turkey	Quasi-experimental design	Exercise training, supported with follow-up calls at home (1 day a week): moderate intensity PA supported by taking a walk in nature (30 min per day). A physical exercise guide was given to the participants. Duration: 12 weeks	62 Postoperative women undergoing chemotherapy: EG (n = 31) and CG (n = 31).	The number of "very active" individuals and the "total PA level" increased significantly in the EG, but decreased significantly in the CG. This increase in the level of PA its related to good QoL.
Donmez & Kapucu [29], 2017 Turkey	RCT	A clinical and home-based nurse-led physical activity program (PAP) and simple lymphatic drainage (SLD): home visits, twice a week (each session lasted 1hour). Duration: 6 weeks	52 breast cancer patients: PAP and SLD (n = 25) and CG (n = 27)	Lymphedema-related symptom severity scores (pain, tension, heaviness, numbness sensation, ADL limitation) have decreased significantly in the EG
Temur & Kapucu [30], 2019 Turkey	RCT	Self-Management of Lymphedema Program: training and training booklet "exercise, massage and prevention methods". Follow-up calls for 6 months and through monthly clinical check-ups. Duration: 6 months	61 breast cancer patients: EG (n = 30), CG (n = 31).	Lymphedema development was not observed in the EG, while 61.2% of the CG developed lymphedema. The QoL of the EG was higher than that of the CG
Zhou et al. [32], 2019 China	RCT	Progressive upper limb exercises and muscle relaxation training (PULE-MRT): before surgery in individual or group format, and following surgery via one-to-one supervision in hospital or home visiting. The exercises were performed in a step-by-step modality and the duration per session ranged from 10 to 30 min, with a frequency of 3 to 6 session per day, for PULE. The duration of the MRT was 30 min per session, twice per day.	Duration: 6 months	102 Breast cancer women following surgery: EG (n = 51) and CG (n = 51) All patients in the EG completed the exercises and training, with 100% of compliance and no adverse events. PULE-MRT had positive effects on improving upper limb function and HRQOL

→

Table 1 cont. Nurse-led exercise interventions

Author and location	Design	Intervention Details	Population	Findings
Wang et al. [31], 2020 China	RCT	Evidence-based nursing (EBN) intervention on upper limb function: pain relief; psychological intervention and health education; massage and traction of the affected limbs (3 times a day for 10 min each time); upper limb rehabilitation exercise (3–5 times per day, with a minimum break between 2 exercises over 2 h and each exercise with a minimum15 min duration). Duration: 6 months	126 Postoperative breast cancer patients undergoing radiotherapy: EG (n = 63) and CG (n = 63)	EBN can positively influence the negative emotional state of BC patients, and it is helpful in reducing the degree of lymph node edema, thereby improving the function of the shoulder joint, and the upper limb function
Li et al. [28], 2016 China	RCT	Home-based, nurse-led health program (NHP): physiological rehabilitation; family-care team provision; emotion-release management (Yoga); informal social support system; follow-up monitoring (online communication, a telephone calls every 2 weeks, a home visit every 2–3 months); and nursing education. Duration: 6 months	226 early-stage cervical cancer patients: EG (n = 119) and CG (n = 107)	NHP improves the scores of QoL scales, cohesion and adaptability subscales, and female sexual function index scales (sexual function or sexual well-being)
Knoerl et al. [18], 2020 USA	Review	Management of chemotherapy-induced peripheral neuropathy (CIPN)-associated physical function deficits: pharmacologic interventions, exercise interventions (various exercise types, dosages, durations, and delivery settings)	Cancer patients with CIPN	Exercise and physical therapy may be promising treatments (e.g., improving strength and balance), but the efficacy and optimal dose of such treatments for CIPN are unclear
Metin & Donmez [19], 2016 Turkey	Review	Dyspnea management: pharmacological interventions (opioids, anticholinergics and Beta2-agonists, anxiolytics and diuretics); nonpharmacological approaches (oxygen, fun, exercise, pulmonary rehabilitation, acupuncture, acupressure and Cognitive Behavioural Therapy)	Cancer patients with dyspnea	Morphine is the most common opioid used to relieve dyspnea. Benzodiazepines reduced anxiety-induced dyspnea. Acupuncture, acupressure, neuromuscular electrical stimulation, external nasal dilator strips, pulmonary rehabilitation, regular exercise programs, use of supplemental oxygen and fun have been reported to manage dyspnea. Nurse counselling, effective respiratory-cough exercises, patient education programs, relaxation techniques and coping strategies also have been effective
Liu et al. [24], 2019 China	Meta--analysis	Breathing exercises: abdominal breathing, pursed-lip breathing, diaphragmatic breathing exercises, thoracic breathing training, volume-oriented incentive spirometer (diversities in the characteristics of interventions). Duration: from 1 week to 12 weeks	870 Lung cancer patients	15 RCT were included. Breathing exercises had positive effects on dyspnea and 6MWD, but not on anxiety and depression. In the surgery subgroup, these exercises could significantly improve dyspnea and 6MWD
Wang et al. [42], 2019 China	Meta--analysis	Home-based exercise training (HBET): aerobic training, resistance training, or a combination of both, and breathing exercises at home and including regular follow-up via home visit, telephone or logbook Duration: from 4 weeks to 16 weeks	453 patients with lung cancer	10 articles met the inclusion criteria. HBET was found to increase 6MWD and improve anxiety. No improvements in dyspnea, depression or HRQOL were observed

→

Table 1 cont. Nurse-led exercise interventions

Author and location	Design	Intervention Details	Population	Findings
Saetan et al. [23], 2020 Thailand	Quasi-experimental study (pre-to--post-test)	Respiratory Rehabilitation Program (RRP): dyspnea education, breathing exercise, using handheld fans, effective coughing, respiratory strengthening training and follow-up by phone (5–10 min) in the third and sixth week. Duration: 8 weeks	28 NSCLC Patients (stage 4): EG (n = 14) and CG (n = 14)	There were significant differences in the mean score of perceived self-efficacy and dyspnea between groups
Liu et al. [43], 2021 China	Non-randomized concurrent-control study	Early ambulation within 2 h after thoracoscopic surgery: patients were encouraged to walk independently for 5–10 min under supervision. On the following days: walk in the corridor for 10 min at least thrice a day. Patients received the standard care as the CG (e.g., back-slapping, effective cough and deep breathing exercises).	227 Patients with lung cancer: OG (n = 100) and CG (n = 127)	83% of patients were able to walk any distance within 2h of extubation, and no adverse events occurred in patients. The length of hospital stay was significantly shorter in the OG than in the CG
Banda et al. [25], 2021 Taiwan	Systematic review and Meta-analysis	Swallowing exercises to improve swallowing function: including jaw, tongue, laryngeal and pharyngeal exercises. The number of sessions ranged from 2–5 per day, with a frequency of 1–15 times per day or weekly. The total duration of exercises ranged from 10 min to 2 hours per day. Duration: from 6 weeks to one year	1100 HNC patients undergoing multimodal treatment	19 RCTs were included for review. Swallowing exercises had a significant small effect on swallowing function, a moderate effect on mouth opening immediately after intervention and a small effect at the 6-month follow-up. Non-significant effects were observed on risk of aspiration, performance status and all domains of QoL
Zeng et al. [26], 2021 China	RCT	Rehabilitation exercises on swallowing function (mouth opening exercises, neck massage, oral organ coordination training, and direct feeding training); oral and pharyngeal nursing (swallowing therapeutic apparatus with frequency of 30–80 Hz, wave width of 700 ms, and current intensity of 0–25mA, for 30 min/time, once/day, and continued for 2 weeks); psychological nursing (relieve anxiety and fear and give psychological comfort) Duration: during radiotherapy	109 esophageal cancer patients undergoing radiotherapy: CG (n = 45) and EG (n = 64)	This intervention can ameliorate dysphagia and improve the QoL. The incidence of complications in the EG was lower than the ones showed in the CG
Ann [41], 2016 Australia	Review	Managing symptom effects of cerebral edema: medication (corticosteroids, antiepileptics), rehabilitation, communication, patient and family education	Patients with high-grade glioma	16 records were selected. While medication is the primary management for symptom clusters, other therapies such as rehabilitation are used to aid in symptom relief and management, improving functionality and QoL, and reducing hospital admissions. Effective communication is needed to the patient and their family to ease coping with symptoms

6MWD — 6-minute walking distance; ADL — activities of daily living; BC — breast cancer; CG — control group; CIPN — chemotherapy induced peripheral neuropathy; CRF — cancer-related fatigue; EG — experimental group; HRQoL — health related quality of life; NHP — nurse-led health program; NSCLC — non-small cell lung cancer; OG — observational group; PA — physical activity; QoL — quality of life; RRP — respiratory rehabilitation program; UC — usual care

mainly among patients with breast cancer or breast cancer survivors. So, specific intervention modes may be more effective for treating CRF at different points in the cancer treatment trajectory [17].

Other studies in this review showed that exercise and physical therapy may be promising treatments for the management of chemotherapy-induced peripheral neuropathy [18] and that they help with dyspnea [19], in addition to fatigue management [20–22].

The respiratory rehabilitation programs provide knowledge on dyspnea and are used to prepare patients with low to moderate dyspnea to manage this symptom [23]. In addition, breathing exercises have positive effects not only on dyspnea but also on the 6-minute walking distance (6MWD) test [24].

Results from 2 studies on swallowing exercises showed that these interventions had effects on swallowing function and on mouth opening in head and neck cancer patients [25], and that can ameliorate dysphagia in esophageal cancer patients, with improvements in QoL [26].

An RCT on using exercise facilities in the community, which included aerobic, resistant, flexible, and pelvic floor muscle interventions, was conducted on prostate cancer survivors, to reduce the complications after treatment, and statistically significant improvements in sexual function were reported [27]. Similarly, home-based physiological rehabilitation along with nursing education, for postoperative patients with early-stage cervical cancer, improved female sexual function or sexual well-being [28].

Concerning lymphedema of the upper extremity in breast cancer patients, Dönmez and Kapucu [29] found benefits for those who were included in a physical activity program and simple lymphatic drainage, reducing lymphedema-related symptom severity scores. In another study conducted by Temur and Kapucu [30] a self-management lymphedema program has been effective preventing lymphedema development in the intervention group. Two RCTs on upper limb exercise following breast cancer surgery were conducted aiming to improve function. Results showed that an evidence-based nursing intervention can reduce the degree of lymph node edema during radiotherapy, thus improving upper limb function [31]. In addition, progressive upper limb exercises and muscle relaxation training had positive effects on HRQoL [32].

Other studies focused on physical function and QoL, showing a significant beneficial effect with supervised exercise interventions. The effects of unsupervised exercise interventions on physical function were better when prescribed at a higher weekly energy expenditure [33]. A systematic review and meta-analysis showed an overall small effect of moderate-to-vigorous physical activity that employs broad-reach approaches, such as for walking steps, supporting these interventions [34].

Some studies reported a practice of exercise where the patients rely on web/online support and health information programs, with variations in levels of patient adherence. Sotirova et al. [35] developed a systematic review and narrative synthesis, in which they concluded that increased acceptability and user satisfaction were associated with interventions seen as time and cost-efficient. Exercise training, supported with follow-up calls at home was found acceptable because it removed traditional barriers to exercise [36]. In a walking intervention (online) conducted by Frensham et al. [37], there was a large increase in steps per day at 12 weeks, but changes were not maintained at 3-month follow-up. However, exercise interventions supported by internet programs or by phone calls also showed improvements in exercise capacity, which is related to good QoL [38–40].

A review provided evidence of how rehabilitation helps relieve and manage symptoms of cerebral edema in patients with high-grade glioma, in addition to medication, communication strategies, and patient and family education, which resulted in improving functionality and QoL and reducing hospital admissions [41].

Exercise programs were further used for the control of anxiety [42], to reduce the length of hospital stay (by encouraging early ambulation after surgery) [43], or to accept and engage in regular activity [36–38].

The studies included in this review evidenced nurse-led exercise programs with some differences (content, frequency, duration, intensity, and degree of supervision) often coupled with other interventions. Therefore it is difficult to evaluate the benefits of exercise alone. However, positive outcomes were linked to exercise and included better physical performance, symptom management, and, consequently, QoL.

Psychoeducational interventions and/or counseling meetings

Most of the studies included in this category (38.1%) were face-to-face sessions, followed by both in-person and telephone/internet contact (28.6%) with cancer patients as part of the nurse's interventions. Only 2 studies, with breast cancer patients, used a group intervention model.

The content of nurse-led interventions comprised in this category varied across studies and most of them incorporated a multifaceted strategy. Some interventions focused on a specific symptom, others on a cluster of symptoms, or covered other challenges (e.g., QoL, return to work) (Tab. 2).

An RCT performed by Fenlon et al. [44] demonstrated the effectiveness of cognitive-behavioral therapy (CBT) in decreasing hot flushes and night sweats in

breast cancer patients. Another study showed that CBT and cognitive training had promising results on cognitive dysfunction (e.g., memory efficacy) [45]. Results of a behavioral intervention conducted by Hunter et al. [46] showed a reduction of anticipatory nausea and vomiting during chemotherapy in patients receiving mindfulness relaxation or relaxing music.

Nurses' interventions in cancer patients can include psychotherapeutic strategies, such as the hope therapy, which seemed promising in producing both physical and psychological benefits [47], or the positive behavior management model, with a significant impact on self-efficacy, hope levels, and QoL scores [48]. An RCT conducted by Zhou et al. [49], on cyclic adjustment training had positive effects on improving psychological resilience. Another study obtained similar results while using a hospital-family holistic care intervention based on "Timing It Right" [50].

Nurses also need training in spiritual care competencies as evidenced in a study performed by Guo et al. [51], where it was observed that patients having lower preferences for nurse spiritual therapeutics, often report an imbalance of their body, mind and spirit, and may need extra effective measures to promote their psychological capital (self-efficacy, optimism, hope, and resilience) and QoL.

Individual psychoeducational programs, linked to cognitive therapy strategies, showed to be effective in reducing psychological symptoms of distress, anxiety, and depression, 12 months after diagnosis [52]. Nurses can use internet-based learning and self-management programs targeting anxiety and depression to provide helpful information and as a complement to standard care, but only for people with milder problems [53]. Another strategy used by Borji et al. [54] was the eye movement desensitization and reprocessing technique, which had significant results in decreasing patient stress. Byun et al. [55] also showed significant changes in distress and mood using a crying therapy program in breast cancer survivors.

An individually tailored nursing intervention that supports self-management of symptoms using motivational interviewing significantly reduced overall symptom distress and severity in cancer patients undergoing chemotherapy [56]. In an ethnographic study, Cerna et al. [57] identified three categories of nursing strategies that support self-management in pelvic-cancer rehabilitation patients: encouraging self-reflection, tailoring solutions together, and keeping patients motivated.

A nurse-led survivorship model of care may be a supportive intervention for lymphoma patients who had finished treatment because, as concluded by Taylor et al. [58], survivors need individualized and tailored support and resources that can promote self-management.

Other studies utilized some form of educational approach and showed positive effects, for example, the educational technology presented by Perdigão et al. [59] with validity for health education regarding fatigue. An educational respiratory rehabilitation animation showed to be effective for promoting training-related knowledge and exercise compliance, with lower complications due to pulmonary surgery [60]. Similarly, a home-based educational program for breathlessness management resulted in the improvement of patients' breathlessness and anxiety [61]. In addition, educational and counseling nutritional interventions after esophageal cancer surgery empowered patients to develop high levels of bodily consciousness and skills in self-management, re-embodying eating [62].

Research on fitness to work is needed because a study conducted by Zeng et al. [63] showed that breast cancer survivors reported higher levels of cognitive limitations at work, anxiety, and lower levels of work productivity and QoL. So, a rehabilitation nurse should ponder strategies to help the patient manage anxiety and to best accommodate specific cognitive limitations and work tasks.

Hospital-based rehabilitation counseling programs showed positive effects on women surgically treated for gynecological cancer, achieving their expected or much-higher goals, but some of them needed additional support [64]. Similarly, in a nurse-led sexual rehabilitation program conducted by Bakker et al. [65] on gynecologic cancer patients treated with pelvic radiotherapy (RT), in-person counseling sessions resulted in sexual function improvement.

Complementary and alternative medicine therapies

Complementary and alternative medicine (CAM) can include a variety of medical products and practices that are not part of standard medical care. Specifically, cancer care CAM comprises the patient's mind, body, and spirit, and includes multidisciplinary approaches (Tab. 3).

The National Cancer Institute [66] believes that evidence-based complementary medicine modalities could be included as part of standard cancer treatment for all patients during the cancer care continuum.

Yangöz and Özer [67] found that music had a moderate effect on the intensity of the pain experienced by patients with cancer-related pain and that this intervention had no adverse effects.

Massage therapy at the end of the chemotherapy treatment, simultaneously with soothing music, showed to be effective in reducing significantly progressive symptoms of pain, fatigue, and sleep disorders' intensity and improving sleep quality over time [68].

A systematic review performed by Baviera et al. [69] assessed the effect of acupuncture on chemotherapy-in-

Table 2. Nurse-led Psychoeducational interventions and/or counselling meetings

Author and location	Design	Intervention Details	Population	Findings
Goldschmidt et al. [52], 2017 Denmark	Randomized pilot study	Individually tailored nurse-navigation intervention (ITNNI): individual, manual-based counselling based on strategies from cognitive therapy and psychoeducation (empathetic listening and dialog, collaborative empiricism, assessment of needs from patient reported outcome measures and dialogue with the patient, goal-setting, intervention plan and debriefing). 1st session conducted face-to-face, while the following sessions were either face-to-face or by telephone. Duration: 12 months	116 Women with newly diagnosed BC (pre-operative): OG (n = 66); EG (n = 25) and CG (n = 25)	This pilot study shows promising feasibility including high participation rate and satisfaction with the ITNNI. No significant effects were observed after 6 months, but results showed statistically significant effects on distress, anxiety and depression, but not on HRQoL, 12 months after diagnosis
Coolbrandt et al. [56], 2018 Belgium	Quasi-experimental study	CHEMO-SUPPORT intervention: one in-person coaching session at the start of treatment, one telephone-based coaching session during the first few days at home, patient information brochure and an online or on-call nursing service for help patients to adequately self-manage their symptoms. Duration: 12 weeks	143 cancer patients starting their first chemotherapy treatment: CG (n = 71) and EG (n = 72)	An individually tailored nursing intervention that supports symptom self-management using motivational interviewing significantly reduces overall symptom distress and symptom severity. Self-efficacy and outcome expectation were significantly higher in the EG. Self-care was statistically similar in both groups
Taylor et al. [58], 2019 Australia	RCT	Care After Lymphoma trial: 3 face-to-face appointments (60 min) in the nurse-led lymphoma survivorship clinic, an individual Survivorship care plan and treatment summary and resource pack. Duration: 6 months	60 Lymphoma participants 3 months post-treatment follow-up: CG (n = 30) and EG (n = 30)	Although not statistically significant, EG reported less unmet needs, less distress and an increase in empowerment, compared with CG. Survivors require individualized and tailored support and resources
Hol et al. [64], 2019 Denmark	Observational cohort study	Hospital-based rehabilitation counselling program: 2 face-to face sessions that lasted up 1hour (1 and 3 months after discharge) and 2 phone calls (1 month after each rehabilitation session) Duration: 5 months	151 women surgically treated for gynaecological cancer (endometrial, ovarian and cervical cancer)	70% of participants at the first phone call and 72% at the second phone call achieved their goals as expected or more or much more than expected. Endometrial cancer patients more often achieved their goals than others
Zhang et al. [50], 2020 China	RCT	Hospital-family holistic care intervention based on "Timing It Right". The phases of the disease were adjusted to the following: the disease diagnosis phase, the perioperative phase, the discharge preparation phase and the adjustment and adaptation phase. The interventions were implemented in both in-hospital (first two phases) and out-of-hospital sites (last three phases). Duration: 6 months	119 Colorectal cancer patients with permanent colostomy: EG (n = 60) and CG (n = 59)	After intervention, there were significant differences in psychological resilience, self-care ability, complications and QoL between groups, at different observation points
Chan et. [47], 2019 China	Pre-to-post design	Brief Hope Intervention consisted of 4 one-on-one sessions: 2 face-to-face sessions (1 hour) and 2 (30 min) telephone follow-up sessions in between. There were 3 core features in the hope therapy: goal thoughts, pathway thoughts and agency thoughts	40 rehabilitation cancer patients	Participants had significant improvement in all aspects of the memorial symptom assessment scale, but the changes in present hope and depression scores were insignificant.

→

Table 2 cont. Nurse-led Psychoeducational interventions and/or counselling meetings

Author and location	Design	Intervention Details	Population	Findings
Hao et al. [48], 2020 China	RCT	Positive behaviour management model based on cognitive framework: reshape the cognitive system (20 min), health-related cognitive structure (90 min), physical and mental relaxation cognitive intervention (10 min) and family members' participation in cognitive management (30 min). Conducted every day. Duration: 2 weeks	84 Breast cancer patients following surgery: EG (n = 42) and CG (n = 42)	After the intervention, self-efficacy and hope level of the EG were significantly higher than those of the CG. Similar results were found for the QoL scores in all aspects
Hauffman et al. [53], 2017 Sweden	RCT	Internet-based learning and self-care program, that combines information, self-care aids and psychosocial support. Duration: 24 months	39 patients with breast, colorectal or prostate cancer, reporting symptoms of anxiety and depression	Participants acknowledged that self-management programs targeting anxiety and depression should be used only by people with milder problems and that severe mental health problems should be handled face-to-face. The use of this program was satisfactory
Zhou et al. [49], 2019 China	RCT	Psychological rehabilitation intervention: cyclic adjustment training (CAT) delivered via a mobile device (comprising 4 steps: confront, pre-introspect, adjust and re-introspect) Duration: 12 weeks	132 Post-surgical breast cancer patients: EG (n = 66) and CG (n = 66)	The CAT had positive effects on improving psychological resilience and reducing the symptoms of anxiety and depression
Cerna et al. [57], 2019 Sweden	Ethnographic study	Three categories of nursing strategies that support self-management of radiation-induced bowel and bladder issues: encouraging self-reflection, tailoring solutions together and keeping patients motivated	Pelvic-cancer rehabilitation patients	Nurses and patients jointly make sense of patients' symptoms and they can co-create solutions tailored to each patient´s individual needs, as well as develop routines to keep the patient motivated in carrying out the devised solutions
Zeng et al. [63], 2017 China	Cross-sectional study	Assessment of levels of distress (anxiety and depression) and cognitive symptoms at work	412 participants: breast cancer survivors (n = 159) vs women with no cancer (musculoskeletal pain) (n = 253)	Higher anxiety and cognitive limitations at work were associated with work limitations and QoL in the breast cancer group only. Depressive symptoms were significantly associated with work limitations in the non-cancer group
Byun et al. [55], 2020 Korea	Pre-post-teste quasi-experimental design	Crying therapy program comprising three-phase: introductory (week 1), execution (week 2), and closing phase (week 3), each of which lasted 2 hours Duration: 3 weeks	27 Breast cancer survivors	Results showed significant changes in distress, mood changes, and immunoglobulin G and smaller changes in blood pressure postintervention. Fatigue and cortisol showed no significant changes
Guo et al. [51], 2021 China	Cross-sectional survey	Spiritual care competencies: preferences for nurse spiritual therapeutics (PNST)	208 cancer patients	Patients with mild-moderate PNST experience lower psychological capital and QoL than patients with high PNST. Psychological capital significantly correlates with QoL of cancer patients

→

Table 2 cont. Nurse-led Psychoeducational interventions and/or counselling meetings

Author and location	Design	Intervention Details	Population	Findings
Von Ah & Crouch [45], 2020 USA	Integrative review	Cognitive rehabilitation for cognitive dysfunction: cognitive behavioural therapy (CBT) and cognitive training (CT — structured practice on cognitive tasks)	1543 Cancer survivors (46% breast cancer)	27 manuscripts were identified for review. CBT and CT appear feasible to deliver, satisfactory to participants, and have shown promising results (e.g., perceived cognitive function, memory efficacy)
Fenlon et al. [44], 2020 United Kingdom	RCT	CBT for the alleviation of hot flushes and night sweats (HFNS): stress management, paced breathing, cognitive and behavioural strategies and maintaining changes. Intervention arm participants attended weekly group CBT session (90 min) Duration: 6 weeks (26 weeks after randomization)	130 Breast cancer patients: CBT group (n = 63) and CT (n = 67)	Results showed a 46% reduction in the mean HFNS problem rating score in the CBT arm and a 15% reduction in the usual care arm. Secondary outcomes (frequency of HFNS, sleep, anxiety and depression) improved significantly
Borji et al. [54], 2019 Iran	Semi-experimental study	Home care using Eye movement desensitization and reprocessing technique for decreasing patients' stress, which included 2 sessions (each session lasted for 45 to 60 min)	60 Gastrointestinal cancer patients: EG (n = 30) and CG (n = 30).	No statistically significant difference was observed between the 2 groups before the intervention in terms of patients' perceived stress. The efficacy and perceived distress of the EG was decreased significantly after the intervention
Hunter et al. [46], 2020 USA	RT	Behavioural intervention (20 min): mindfulness relaxation (MR — single exercise, composed of guided mindfulness, imagery, and relaxation practices) or relaxing music (RM — recording consisted of relaxing music with nature sounds or a vocal track), for reduction of anticipatory nausea and vomiting (ANV) Duration: 4 or 6 course chemotherapy protocol	474 Patients undergoing chemotherapy for solid tumours (85% BC): MR (n = 160), RM (n = 159) or standard care (n = 155)	Compared to standard care, there was reduced anticipatory nausea at the midpoint of chemotherapy in those receiving MR and RM. There was no difference between treatment groups in ANV at the end of chemo and post chemotherapy nausea and vomiting at either time point
Bakker et al. [65], 2017 Netherlands	Observational pilot study	Nurse-led sexual rehabilitation after RT: 4 face-to-face counselling sessions at 1, 2, 3 and 6 months following radiotherapy (RT) or brachytherapy (BT). Information booklet and a vaginal dilator set were provided. Couples' mutual coping and support processes were promoted. Duration: 12 months	20 gynaecologic cancer patients treated with combined pelvic RT and BT	Sexual function improved between 1 and 6 months after RT, with additional improvement at 12 months. At 6 months, 88% of participants reported using dilators at least twice a week, and partnered patients gradually replaced or supplemented vaginal dilator use by having sexual intercourse. Most participants reported the nurses had adequate expertise and counselling skills
Missel et al. [62], 2018 Denmark	Qualitative study — phenomenological approach	Education and counselling nutritional intervention: 4 sessions between the patient and a nurse. Duration: Preoperatively to 2 weeks after discharge	10 patients after curative surgery for esophageal cancer	The essence of experiencing the education and counselling intervention can be structured into 3 themes: embodied disorientation; living with increased attention to bodily function and re-embodying eating. The intervention empowered the patients to regain some control of their own bodies in an effort to regain agency in their own lives

→

Table 2 cont. Nurse-led Psychoeducational interventions and/or counselling meetings

Author and location	Design	Intervention Details	Population	Findings
Li et al. [60], 2021 China	RCT	The respiratory rehabilitation (RR) animation was downloaded on an iPad, and consisted of 3 sections totalling 31 min: 6-min animation introduction, a 10-min nurse demonstration, and a 15-min patient teach back demonstration. It was performed twice each day at the patient´s bedside.	80 postsurgical lung cancer patients: EG (n = 40) and CG (n = 40).	Educational animation is effective for promoting training-related knowledge and exercise compliance with active RR. Mean scores of training-related knowledge and exercise compliance in the EG were higher than those of the CG. Postoperative pulmonary complications were lower, and 6MWD was longer compared with the CG
Choratas et al. [61], 2020 Cyprus	Feasibility RCT	Home-based educational programme for breathlessness management consisted of a PowerPoint presentation (with 2 video recordings and a practical exercise) and implementation of 3 non-pharmacological interventions: diaphragmatic breathing, inspirational muscle training, and use of a handheld fan (lasted about 30-50 min, applied twice to the EG after the 1st and 2nd assessment). Duration: 4 weeks	19 Lung cancer patients and 19 family caregivers (f.c.): EG (n = 11+11) and CG (n = 8+8)	There was a reported improvement in the EG patients´ breathlessness and anxiety levels, as well an improvement in the anxiety and burden levels of their f.c.
Perdigão et al. [59], 2019 Brazil	Methodological study	Educational technology (ET): "Knowing and coping with fatigue" and non-pharmacological strategies for the management of this symptom (physical exercise practice, sleep hygiene, energy conservation and behavioural intervention)	Cancer patients undergoing outpatient chemotherapy	The ET presented content and appearance validity for health education regarding fatigue

6MWD — 6-minute walking distance; BC — breast cancer; BT — brachytherapy; CAT — cyclic adjustment training; CBT — cognitive behavioural therapy; CG — control group; CT — Cognitive training; EG — experimental group; ET — educational technology; f.c. — family caregivers; HFNS — hot flushes and night sweats; HRQoL — health related quality of life; ITNNI — individually tailored nurse-navigation intervention; NSCLC — non-small cel lung cancer; OG — observational group; PNST — preferences for nurse spiritual therapeutics; QoL — quality of life; RR — respiratory rehabilitation; RT — radiotherapy; RT — randomized trial

duced peripheral neuropathy symptoms. Despite the variety of intervention dimensions, an improvement in peripheral neuropathy was observed without any side effects. Izgu et al. [70], also showed beneficial effects on the prevention of peripheral neuropathic pain in breast cancer patients receiving adjuvant paclitaxel, by using a classical massage intervention.

The symptoms of fatigue experienced by patients during cancer treatment can be managed at home with reflexology or meditative practices [71]. In addition to fatigue improvement, reflexology associated with sleep hygiene education has proven to be effective in increasing sleep quality [72].

Discussion

Comprehensive rehabilitation care is needed as a standard part of cancer care. According to Alfano and Pergolotti [7], its assessment must include a whole-person view of functioning, disability, and health, aiming toward improving function in activities and improving a patient's capacity to participate completely in life roles, such as work or leisure.

Nurses are recognized as extremely skilled and experienced health professionals who incorporate evidence-based literature into action, improving the quality of care and their patients' outcomes. Three categories of nurse-led interventions were identified within this scoping review, focused on cancer rehabilitation from the diagnosis.

Conceptual models and theories serve as a guide for clinical practice, and this review incorporates elements of Orem's Self-care deficit nursing theory [10]. Considering the theory of nursing systems, the analyzed nurse-led rehabilitation interventions are mainly supportive-educative. In the supportive-educative system, the nurse's role is to encourage and support the person as a self-care agent, as the patient tries to achieve all stages of self-care [10].

Table 3. Nurse-led complementary and alternative medicine therapies

Author and location	Design	Intervention Details	Population	Findings
Miladinia et al. [68], 2016 Iran	RCT	Massage therapy: slow-stroke back massage (SSBM) 3 times a week for 10 min at the end of the chemotherapy treatment. An audio CD containing soothing music was also used during SSBM intervention. Duration: 4 weeks	60 patients with acute leukaemia undergoing chemotherapy: EG (n = 30) and CG (n = 30)	SSBM intervention significantly reduced progressive symptoms of pain, fatigue and sleep disorders intensity, and improved sleep quality over time
Izgu et al. [70], 2019 Turkey	RCT	Classical Massage was applied to the patient before each paclitaxel infusion, once a week, totally 12 sessions (room with a controlled temperature 20-22°C). Massage lasting for 30 min in each session: 20 min for the feet and 10 min for the hands. Duration: 16 weeks	Breast cancer patients receiving adjuvant paclitaxel: EG (n = 19) and CG (n = 21)	The peripheral neuropathic pain was lower in the EG, compared to the CG at week 12. Classical massage improved the QoL and showed beneficial effects on the nerve conduction studies findings
Zengin & Aylaz [72], 2019 Turkey	Pre-to-post design	Reflexology (16 sessions of 30 min) and sleep hygiene education (3 sessions of 20 min). Duration: Reflexology (8 weeks, with 2 sessions per week) and sleep hygiene (3 weeks)	167 adult cancer patients undergoing chemotherapy: EG (n = 84) and CG (n = 83)	Patients in the EG reported increased sleep quality and reduced fatigue
Wyatt et al. [71], 2021 USA	SMART sequential multiple assignment randomized trial	Home-based reflexology and meditative practices: after the first 4 weeks in the two intervention groups, patient´s response on fatigue was determined. Dyads with nonresponding patients were randomized for the second time to either continue with the same therapy for more 4 weeks, or add 4 weeks of another therapy. Duration: 12 weeks	Cancer patients and informal caregivers (dyads = 347): reflexology (n = 150), meditative practices (n = 150) or control (n = 47)	Sequences of reflexology and meditative practices were not different in symptom outcomes. Participants who used reflexology for the full 8 weeks had lower summed severity index compared to those who started with reflexology and added meditative practices after the first 4 weeks
Baviera et al. [69], 2019 Brazil	Systematic review	Acupuncture characterized by a variety of intervention dimensions (type of protocol, use of medications, time of treatment, and different outcomes measures) Duration: from only a few weeks to 14 weeks	Adult cancer patients with chemotherapy-induced peripheral neuropathy symptoms	4 cohort studies and 1 quasi-experimental study included. Evidence suggested that acupuncture was associated with an improvement in the peripheral neuropathy, and had no side effects
Yangöz & Özer [67], 2019 Turkey	Systematic review and Meta-analysis	Music intervention: passive listening method, which ranged from 30 to 60 min and 1 to 3 sessions	593 patients with cancer-related pain (CRP)	6 RCTs included. It was found that music interventions had a moderate effect on CRP, and no adverse events were reported

CG — Control group; CRP — cancer-related pain; EG — experimental group; SSBM — slow-stroke back massage

Many of the included studies targeted several outcomes, to manage cancer-related symptoms or improve QoL. The intensity and type of cancer rehabilitation interventions need to be personalized to achieve desired outcomes: restoring function, improving participation, and/or preventing late adverse effects of cancer treatment [7].

As stated previously, CRF was the most targeted symptom, maybe because it is the most common side effect of cancer and its treatments, and it can frequently persist for months or years. Research on fatigue in cancer patients included mainly self-reports of fatigue, with a lack of data exploring biologic or physiologic correlates [73], and it is also evident in studies included in the review.

Several studies focused on rehabilitation interventions in breast cancer patients and even though they contribute to developing rehabilitation knowledge and clinical practice, additional research is needed for people with other types of cancer, as each diagnosis and treatment may create various burdens for the patient. Not many articles included patients with hematologic malignancies. In addition, studies with advanced

cancer patients in palliative care were scarce in this review. According to Lee et al. [74], advanced cancer patients hospitalized in hospice palliative care units face numerous problems, such as QoL complications and limitations in performing daily activities, which comprehensive rehabilitation interventions can help resolve. So, cancer rehabilitation is crucial at various stages for cancer patients, including in the palliative care phase.

Some other areas could benefit from further attention, such as nutrition or dysphagia, to identify patient-specific needs and interventions and to prevent or control serious disorders, such as cachexia. In addition, it is necessary to gather evidence on the effectiveness of interventions to promote patient employment or return to work and to improve cognitive functioning.

In a study conducted by Smith et al. [75], it was concluded that exercise can be a vital aspect of a patient's treatment and survivorship. Even moderate levels of supervised exercise can provide beneficial physical and psychological outcomes. Thus, incorporating exercise into the routine of a person with cancer provides benefits to their QoL and it is important for muscular and aerobic fitness, both during and after treatment [76]. Studies included in the review also demonstrated that exercise had positive effects, not only on physical function and QoL but also had psychological benefits. Additionally, exercise could be effective in the management of treatment side effects. Thus, according to Segal et al. [77], cancer patients can be allowed to determine the kind of exercise that they would prefer to do for aerobic and resistance training. Finally, the intensity of the exercise must be adjusted for each patient, then increased slowly in the continuum of treatment, and it should be closely monitored by health professionals [78].

In addition to exercise, the other two categories of intervention also showed positive trends. Most of the psychoeducational interventions or counseling meetings had promising results. With regard to many CAM treatments and their hoped-for benefits, reliable scientific evidence is needed in terms of their safety and effectiveness.

Limitations

Although there are limitations in this scoping review, it does provide a good start for nurses working in cancer rehabilitation. In addition, this article provides a departure point for researchers who need to study the effectiveness of rehabilitation-specific interventions. Several problems seen in the cancer care continuum were identified, including the survivorship period. Even if the results from the studies were variable and showed clinically positive trends, they do not always have a statistical significance and could not be generalized to larger populations. The discrepancies found between different results can be attributed to the timing when the intervention was delivered to patients, the duration of the intervention or the follow-up, and the focus of each study. So, comparisons between studies may be hard. Another limitation is that some studies had small samples.

Additional research is needed to develop and validate the effects of cancer rehabilitation interventions on patient outcomes, including the efficacy of cancer treatments strategies, prevention of their side effects, and cancer patients' reactivation.

Conclusions

Cancer rehabilitation is becoming more and more important in different categories (prevention of late effects of treatment, restoring function and enhancing participation) to improve the QoL in cancer patients.

Nurses, as part of the rehabilitation team, play an instrumental role in providing the highest level of patient-centered care with individualized interventions to prevent, manage or alleviate cancer-related symptoms or challenges. These rehabilitation providers deliver evidence-based direct care, psychological support, cancer patient/caregiver education, care coordination, and health promotion, across all stages of the disease.

The main nurse-led interventions in cancer patients included both exercise/physical activity and psychoeducation/counseling sessions. The beneficial effects of these interventions were recognized, but this is still insufficient. More research is needed to help create more rehabilitation programs for specific cancer stages and diagnoses.

Conflict of interest

The authors declare no conflict of interest.

Funding

No external funding.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69(1): 7–34, doi: 10.3322/caac.21551.
2. John RM. Global Cancer Facts & Figures 4 th Edition-Special section,the obesity epidemic. American Cancer Society. 2018; 76.
3. World Health Organization (WHO). Cancer. 2020. https://www.who.int/news-room/fact-sheets/detail/cancer.
4. World Health Organization. Rehabilitation in health systems: guide for action. Licence: CC BY-NC-SA 3.0 IGO. 2019.
5. Padgett LS, Asher A, Cheville A. The Intersection of Rehabilitation and Palliative Care: Patients With Advanced Cancer in the Inpatient Rehabilitation Setting. Rehabil Nurs. 2018; 43(4): 219–228, doi: 10.1097/rnj.0000000000000171, indexed in Pubmed: 29957699.

6. Silver JK. Cancer prehabilitation and its role in improving health outcomes and reducing health care costs. Semin Oncol Nurs. 2015; 31(1): 13–30, doi: 10.1016/j.soncn.2014.11.003, indexed in Pubmed: 25636392.
7. Alfano C, Pergolotti M. Next-Generation Cancer Rehabilitation: A Giant Step Forward for Patient Care. Rehabil Nurs. 2018; 43(4): 186–194, doi: 10.1097/rnj.0000000000000174.
8. Stout NL, Silver JK, Raj VS, et al. Toward a National Initiative in Cancer Rehabilitation: Recommendations From a Subject Matter Expert Group. Arch Phys Med Rehabil. 2016; 97(11): 2006–2015, doi: 10.1016/j.apmr.2016.05.002, indexed in Pubmed: 27237580.
9. Reigle BS, Campbell GB, Murphy KB. Cancer Rehabilitation and the Role of the Rehabilitation Nurse. A White Paper by the Association of Rehabilitation Nurses. Association of Rehabilitation Nurses. 2017: 1–15.
10. Orem DE, Taylor SG, Renpenning KM. Nursing: Concepts of Practice. St Louis, Mosby 2001.
11. Joanna Briggs Institute. JBI Manual for Evidence Synthesis. 2019. https://wiki.jbi.global/display/MANUAL/JBI+Manual+for+Evidence+Synthesis.
12. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7): e1000097, doi: 10.1371/journal.pmed.1000097, indexed in Pubmed: 19621072.
13. Maqbali M, Hughes C, Dunwoody L, et al. Exercise Interventions to Manage Fatigue in Women With Gynecologic Cancer: A Systematic Review. Oncol Nurs Forum. 2019; 46(1): 71–82, doi: 10.1188/19.ONF.71-82, indexed in Pubmed: 30547952.
14. McGowan K. Physical Exercise and Cancer-Related Fatigue in Hospitalized Patients: Role of the Clinical Nurse Leader in Implementation of Interventions. Clin J Oncol Nurs. 2016; 20(1): E20–E27, doi: 10.1188/16.CJON.E20-E27, indexed in Pubmed: 26800418.
15. Scott K, Posmontier B. Exercise Interventions to Reduce Cancer-Related Fatigue and Improve Health-Related Quality of Life in Cancer Patients. Holist Nurs Pract. 2017; 31(2): 66–79, doi: 10.1097/HNP.0000000000000194, indexed in Pubmed: 28181972.
16. Huether K, Abbott L, Cullen L, et al. Energy Through Motion©: An Evidence-Based Exercise Program to Reduce Cancer-Related Fatigue and Improve Quality of Life. Clin J Oncol Nurs. 2016; 20(3): E60–E70, doi: 10.1188/16.CJON.E60-E70, indexed in Pubmed: 27206306.
17. Mustian KM, Alfano CM, Heckler C, et al. Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. JAMA Oncol. 2017; 3(7): 961–968, doi: 10.1001/jamaoncol.2016.6914, indexed in Pubmed: 28253393.
18. Knoerl R, Gilchrist L, Kanzawa-Lee GA, et al. Proactive Rehabilitation for Chemotherapy-Induced Peripheral Neuropathy. Semin Oncol Nurs. 2020; 36(1): 150983, doi: 10.1016/j.soncn.2019.150983, indexed in Pubmed: 31959510.
19. METIN ZG. Dyspnea Management in Patients with Cancer. Turkish Journal of Oncology. 2016, doi: 10.5505/tjo.2016.1366.
20. Wang HL, McMillan SC, Vijayakumar N, et al. A Behavioral Physical Activity Intervention to Manage Moderate and Severe Fatigue Among Head and Neck Cancer Patients-Pre-efficacy Study in the National Institutes of Health ORBIT Model. Cancer Nurs. 2019; 42(1): E1–E14, doi: 10.1097/NCC.0000000000000568, indexed in Pubmed: 29461282.
21. Schumacher MM, McNiel P. The Impact of Livestrong® at the YMCA for Cancer Survivors. Oncol Nurs Forum. 2018; 45(6): 717–725, doi: 10.1188/18.ONF.717-725, indexed in Pubmed: 30339155.
22. Mendes L, Barichello E. INTERVENÇÕES NO MANEJO DA FADIGA E QUALIDADE DE VIDA EM PACIENTES EM QUIMIOTERAPIA: ESTUDO DE REVISÃO. Cogitare Enfermagem. 2019; 24, doi: 10.5380/ce.v24i0.61790.
23. Saetan P, Chaiviboontham S, Pokpalagon P, et al. The Effects of the Respiratory Rehabilitation Program on Perceived Self-Efficacy and Dyspnea in Patients with Lung Cancer. Asian Nurs Res (Korean Soc Nurs Sci). 2020; 14(5): 277–285, doi: 10.1016/j.anr.2020.08.010, indexed in Pubmed: 32916339.
24. Liu T, Feng J, Ge L, et al. Feasibility, safety and outcomes of ambulation within 2 h postoperatively in patients with lung cancer undergoing thoracoscopic surgery. International Journal of Nursing Practice. 2021, doi: 10.1111/ijn.12994.
25. Banda KJ, Chu H, Kao CC, et al. Swallowing exercises for head and neck cancer patients: A systematic review and meta-analysis of randomized control trials. Int J Nurs Stud. 2021; 114: 103827, doi: 10.1016/j.ijnurstu.2020.103827, indexed in Pubmed: 33352439.
26. Zeng X, Li L, Wang W, et al. Rehabilitation Nursing Intervention Can Improve Dysphagia and Quality of Life of Patients Undergoing Radiotherapy for Esophageal Cancer. J Oncol. 2021; 2021: 3711699, doi: 10.1155/2021/3711699, indexed in Pubmed: 34394350.
27. Mardani A, Pedram Razi S, Mazaheri R, et al. Effect of the exercise programme on the quality of life of prostate cancer survivors: A randomized controlled trial. Int J Nurs Pract. 2021; 27(2): e12883, doi: 10.1111/ijn.12883, indexed in Pubmed: 32827200.
28. Li J, Huang J, Zhang J, et al. A home-based, nurse-led health program for postoperative patients with early-stage cervical cancer: A randomized controlled trial. Eur J Oncol Nurs. 2016; 21: 174–180, doi: 10.1016/j.ejon.2015.09.009, indexed in Pubmed: 26482004.
29. Dönmez AA, Kapucu S. The effectiveness of a clinical and home-based physical activity program and simple lymphatic drainage in the prevention of breast cancer-related lymphedema: A prospective randomized controlled study. Eur J Oncol Nurs. 2017; 31: 12–21, doi: 10.1016/j.ejon.2017.09.004, indexed in Pubmed: 29173822.
30. Temur K, Kapucu S. The effectiveness of lymphedema self-management in the prevention of breast cancer-related lymphedema and quality of life: A randomized controlled trial. Eur J Oncol Nurs. 2019; 40: 22–35, doi: 10.1016/j.ejon.2019.02.006, indexed in Pubmed: 31229204.
31. Wang X, Lai Q, Tian Y, et al. Effect of evidence-based nursing intervention on upper limb function in postoperative radiotherapy patients with breast cancer. Medicine (Baltimore). 2020; 99(11): e19183, doi: 10.1097/MD.0000000000019183, indexed in Pubmed: 32176044.
32. Zhou K, Wang W, An J, et al. Effects of Progressive Upper Limb Exercises and Muscle Relaxation Training on Upper Limb Function and Health-Related Quality of Life Following Surgery in Women with Breast Cancer: A Clinical Randomized Controlled Trial. Ann Surg Oncol. 2019; 26(7): 2156–2165, doi: 10.1245/s10434-019-07305-y, indexed in Pubmed: 30972655.
33. Sweegers MG, Altenburg TM, Chinapaw MJ, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2018; 52(8): 505–513, doi: 10.1136/bjsports-2017-097891, indexed in Pubmed: 28954800.
34. Groen WG, van Harten WH, Vallance JK. Systematic review and meta-analysis of distance-based physical activity interventions for cancer survivors (2013-2018): We still haven't found what we're looking for. Cancer Treat Rev. 2018; 69: 188–203, doi: 10.1016/j.ctrv.2018.07.012, indexed in Pubmed: 30077954.
35. Sotirova MB, McCaughan EM, Ramsey L, et al. Acceptability of online exercise-based interventions after breast cancer surgery: systematic review and narrative synthesis. J Cancer Surviv. 2021; 15(2): 281–310, doi: 10.1007/s11764-020-00931-6, indexed in Pubmed: 32930924.
36. Hoffman AJ, Brintnall RA. A Home-based Exercise Intervention for Non-Small Cell Lung Cancer Patients Post-Thoracotomy. Semin Oncol Nurs. 2017; 33(1): 106–117, doi: 10.1016/j.soncn.2016.11.011, indexed in Pubmed: 28062324.
37. Frensham LJ, Parfitt G, Dollman J. Predicting Engagement With Online Walking Promotion Among Metropolitan and Rural Cancer Survivors. Cancer Nurs. 2020; 43(1): 52–59, doi: 10.1097/NCC.0000000000000649, indexed in Pubmed: 30312190.
38. Nemli A, Tekinsoy Kartin P. Effects of exercise training and follow-up calls at home on physical activity and quality of life after a mastectomy. Jpn J Nurs Sci. 2019; 16(3): 322–328, doi: 10.1111/jjns.12243, indexed in Pubmed: 30428503.
39. Chang YL, Tsai YF, Hsu CL, et al. The effectiveness of a nurse-led exercise and health education informatics program on exercise capacity and quality of life among cancer survivors after esophagectomy: A randomized controlled trial. Int J Nurs Stud. 2020; 101: 103418, doi: 10.1016/j.ijnurstu.2019.103418, indexed in Pubmed: 31670173.
40. Zhou K, Wang W, Zhao W, et al. Benefits of a WeChat-based multimodal nursing program on early rehabilitation in postoperative women with breast cancer: A clinical randomized controlled trial. Int J Nurs Stud. 2020; 106: 103565, doi: 10.1016/j.ijnurstu.2020.103565, indexed in Pubmed: 32272281.
41. Ann J, Rn H. Understanding and managing symptom effects of cerebral oedema in high-grade glioma patients : a review of the literature. Neuroscience G. 2016; 17(2): 6–14.
42. Wang YQ, Liu X, Yin YY, et al. Effects of Home-Based Exercise Training for Patients With Lung Cancer. Oncol Nurs Forum. 2019; 46(4): E119–E134, doi: 10.1188/19.ONF.E119-E134, indexed in Pubmed: 31225844.
43. Liu T, Feng J, Ge L, et al. Feasibility, safety and outcomes of ambulation within 2 h postoperatively in patients with lung cancer undergoing thoracoscopic surgery. Int J Nurs Pract. 2021 [Epub ahead of print]: e12994, doi: 10.1111/ijn.12994, indexed in Pubmed: 34318965.
44. Fenlon D, Maishman T, Day L, et al. Effectiveness of nurse-led group CBT for hot flushes and night sweats in women with breast cancer: Results of the MENOS4 randomised controlled trial. Psychooncology. 2020; 29(10): 1514–1523, doi: 10.1002/pon.5432, indexed in Pubmed: 32458473.

45. Von Ah D, Crouch A. Cognitive Rehabilitation for Cognitive Dysfunction after Cancer and Cancer Treatment: Implications for Nursing Practice. Semin Oncol Nurs. 2020; 36(1): 150977, doi: 10.1016/j.soncn.2019.150977, indexed in Pubmed: 31959511.
46. Hunter JJ, Maunder RG, Sui D, et al. A randomized trial of nurse-administered behavioral interventions to manage anticipatory nausea and vomiting in chemotherapy. Cancer Med. 2020; 9(5): 1733–1740, doi: 10.1002/cam4.2863, indexed in Pubmed: 31957269.
47. Chan K, Wong FKY, Lee PH. A Brief Hope Intervention to Increase Hope Level and Improve Well-Being in Rehabilitating Cancer Patients: A Feasibility Test. SAGE Open Nurs. 2019; 5: 2377960819844381, doi: 10.1177/2377960819844381, indexed in Pubmed: 33415238.
48. Hao YJ, Sun HB, Li HW, et al. Application of positive behavior management in patients after breast cancer surgery. World J Clin Cases. 2020; 8(4): 689–699, doi: 10.12998/wjcc.v8.i4.689, indexed in Pubmed: 32149053.
49. Zhou K, Li J, Li X. Effects of cyclic adjustment training delivered via a mobile device on psychological resilience, depression, and anxiety in Chinese post-surgical breast cancer patients. Breast Cancer Res Treat. 2019; 178(1): 95–103, doi: 10.1007/s10549-019-05368-9, indexed in Pubmed: 31342310.
50. Zhang Xi, Gao R, Lin JL, et al. Effects of hospital-family holistic care model on the health outcome of patients with permanent enterostomy based on the theory of 'Timing It Right'. J Clin Nurs. 2020; 29(13-14): 2196–2208, doi: 10.1111/jocn.15199, indexed in Pubmed: 31970830.
51. Guo YF, Wang KF, Cross W, et al. Quality of life in cancer patients with different preferences for nurse spiritual therapeutics: The role of psychological capital. J Adv Nurs. 2022; 78(4): 991–1000, doi: 10.1111/jan.15023, indexed in Pubmed: 34423462.
52. Mertz BG, Dunn-Henriksen AK, Kroman N, et al. The effects of individually tailored nurse navigation for patients with newly diagnosed breast cancer: a randomized pilot study. Acta Oncol. 2017; 56(12): 1682–1689, doi: 10.1080/0284186X.2017.1358462, indexed in Pubmed: 28758822.
53. Hauffman A, Alfonsson S, Mattsson S, et al. The Development of a Nurse-Led Internet-Based Learning and Self-care Program for Cancer Patients With Symptoms of Anxiety and Depression-A Part of U-CARE. Cancer Nurs. 2017; 40(5): E9–EE16, doi: 10.1097/NCC.0000000000000402, indexed in Pubmed: 27223884.
54. Borji M, Tarjoman A, Abdi A, et al. Efficacy of Implementing Home Care Using Eye Movement Desensitization and Reprocessing in Reducing Stress of Patients with Gastrointestinal Cancer. Asian Pac J Cancer Prev. 2019; 20(7): 1967–1971, doi: 10.31557/APJCP.2019.20.7.1967, indexed in Pubmed: 31350952.
55. Byun HS, Hwang H, Kim GD. Crying Therapy Intervention for Breast Cancer Survivors: Development and Effects. Int J Environ Res Public Health. 2020; 17(13), doi: 10.3390/ijerph17134911, indexed in Pubmed: 32646037.
56. Coolbrandt A, Wildiers H, Laenen A, et al. A Nursing Intervention for Reducing Symptom Burden During Chemotherapy . Oncol Nurs Forum. 2018; 45(1): 115–128, doi: 10.1188/18.ONF.115-128, indexed in Pubmed: 29251287.
57. Cerna K, Ivarsson J, Weilenmann A, et al. Supporting self-management of radiation-induced bowel and bladder dysfunction in pelvic-cancer rehabilitation: An ethnographic study. J Clin Nurs. 2019; 28(13-14): 2624–2634, doi: 10.1111/jocn.14849, indexed in Pubmed: 30865355.
58. Taylor K, Chivers P, Bulsara C, et al. Care After Lymphoma (CALy) trial: A phase II pilot pragmatic randomised controlled trial of a nurse-led model of survivorship care. Eur J Oncol Nurs. 2019; 40: 53–62, doi: 10.1016/j.ejon.2019.03.005, indexed in Pubmed: 31229207.
59. Perdigão MM, Rodrigues AB, Magalhães Td, et al. Educational technology for fatigue management related to antineoplastic chemotherapy. Rev Bras Enferm. 2019; 72(6): 1519–1525, doi: 10.1590/0034-7167-2018-0505, indexed in Pubmed: 31644739.
60. Li J, Davies M, Ye M, et al. Impact of an Animation Education Program on Promoting Compliance With Active Respiratory Rehabilitation in Postsurgical Lung Cancer Patients: A Randomized Clinical Trial. Cancer Nurs. 2021; 44(2): 106–115, doi: 10.1097/NCC.0000000000000758, indexed in Pubmed: 31714266.
61. Choratas A, Papastavrou E, Charalambous A, et al. Developing and Assessing the Effectiveness of a Nurse-Led Home-Based Educational Programme for Managing Breathlessness in Lung Cancer Patients. A Feasibility Study. Front Oncol. 2020; 10: 1366, doi: 10.3389/fonc.2020.01366, indexed in Pubmed: 32983967.
62. Missel M, Hansen M, Jackson R, et al. Re-embodying eating after surgery for oesophageal cancer: Patients' lived experiences of participating in an education and counselling nutritional intervention. J Clin Nurs. 2018; 27(7-8): 1420–1430, doi: 10.1111/jocn.14297, indexed in Pubmed: 29399901.
63. Zeng Y, Cheng ASK, Feuerstein M. Cognitive Limitations at Work Among Employed Breast Cancer Survivors in China. Rehabil Nurs. 2017; 42(6): 347–353, doi: 10.1002/rnj.279, indexed in Pubmed: 27278275.
64. Adellund Holt K, Hansen DG, Mogensen O, et al. Self-assessment of Goal Achievements Within a Gynecological Cancer Rehabilitation Counseling. Cancer Nurs. 2019; 42(1): 58–66, doi: 10.1097/NCC.0000000000000567, indexed in Pubmed: 29461281.
65. Bakker RM, Mens JWM, de Groot HE, et al. A nurse-led sexual rehabilitation intervention after radiotherapy for gynecological cancer. Support Care Cancer. 2017; 25(3): 729–737, doi: 10.1007/s00520-016-3453-2, indexed in Pubmed: 27787681.
66. National Cancer Institute. Complementary and Alternative Medicine for Health Professionals. 2020. https://www.cancer.gov/about-cancer/treatment/cam/hp.
67. Yangöz ŞT, Özer Z. The effect of music intervention on patients with cancer-related pain: A systematic review and meta-analysis of randomized controlled trials. J Adv Nurs. 2019; 75(12): 3362–3373, doi: 10.1111/jan.14184, indexed in Pubmed: 31452232.
68. Miladinia M, Baraz S, Shariati A, et al. Effects of Slow-Stroke Back Massage on Symptom Cluster in Adult Patients With Acute Leukemia: Supportive Care in Cancer Nursing. Cancer Nurs. 2017; 40(1): 31–38, doi: 10.1097/NCC.0000000000000353, indexed in Pubmed: 26925992.
69. Baviera AF, Olson K, Paula JM, et al. Acupuncture in adults with Chemotherapy-Induced Peripheral Neuropathy: a systematic review. Rev Lat Am Enfermagem. 2019; 27: e3126, doi: 10.1590/1518-8345.2959.3126, indexed in Pubmed: 30916227.
70. Izgu N, Metin ZG, Karadas C, et al. Prevention of chemotherapy--induced peripheral neuropathy with classical massage in breast cancer patients receiving paclitaxel: An assessor-blinded randomized controlled trial. Eur J Oncol Nurs. 2019; 40: 36–43, doi: 10.1016/j.ejon.2019.03.002, indexed in Pubmed: 31229205.
71. Wyatt G, Lehto R, Guha-Niyogi P, et al. Reflexology and meditative practices for symptom management among people with cancer: Results from a sequential multiple assignment randomized trial. Res Nurs Health. 2021; 44(5): 796–810, doi: 10.1002/nur.22169, indexed in Pubmed: 34515341.
72. Zengin L, Aylaz R. The effects of sleep hygiene education and reflexology on sleep quality and fatigue in patients receiving chemotherapy. Eur J Cancer Care (Engl). 2019; 28(3): e13020, doi: 10.1111/ecc.13020, indexed in Pubmed: 30784127.
73. National Cancer Institute. Fatigue – health professional version. https://www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue--hp-pdq#cit/section_1.2. 2020.
74. Lee CH, Kim JK, Jun HJ, et al. Rehabilitation of Advanced Cancer Patients in Palliative Care Unit. Ann Rehabil Med. 2018; 42(1): 166–174, doi: 10.5535/arm.2018.42.1.166, indexed in Pubmed: 29560337.
75. Smith TM, Broomhall CN, Crecelius AR. Physical and Psychological Effects of a 12-Session Cancer Rehabilitation Exercise Program. Clin J Oncol Nurs. 2016; 20(6): 653–659, doi: 10.1188/16.CJON.653-659, indexed in Pubmed: 27857248.
76. Segal R, Zwaal C, Green E, et al. Exercise for People with Cancer Guideline Development Group. Exercise for people with cancer: a systematic review. Curr Oncol. 2017; 24(4): e290–e315, doi: 10.3747/co.24.3619, indexed in Pubmed: 28874900.
77. Segal R, Zwaal C, Green E, et al. Exercise for People with Cancer Guideline Development Group. Exercise for people with cancer: a clinical practice guideline. Curr Oncol. 2017; 24(1): 40–46, doi: 10.3747/co.24.3376, indexed in Pubmed: 28270724.
78. Song J, Wang T, Wang Y, et al. Evaluation of evidence for exercise intervention in patients with cancer-related fatigue during chemoradiotherapy. J Clin Nurs. 2021; 30(13-14): 1854–1862, doi: 10.1111/jocn.15696, indexed in Pubmed: 33555639.

VIA MEDICA

REVIEW ARTICLE

Anna Kopacz-Bednarska, Teodora Król

Department of Medical Biology, Institute of Biology, Jan Kochanowski University, Kielce, Poland

Cisplatin — properties and clinical application

Address for correspondence:
Anna Kopacz-Bednarska, PhD
Department of Medical Biology, Institute of Biology, Jan Kochanowski University
Uniwersytecka 7 St., 25–406 Kielce, Poland
e-mail: anna.kopacz-bednarska@ujk.edu.pl

Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0020

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Chemotherapy is one of the basic methods of cancer treatment, which uses compounds with a broad spectrum of activity. Among the diverse group of cytostatic drugs, platinum derivatives play an important role in cancer therapy, including cisplatin. Cisplatin is a first generation platinum drug approved in medicine in the 1980s. The mechanism of the anti-tumor activity of cisplatin is based on pro-apoptotic and antiproliferative activity. Cisplatin, through the formation of appropriate adducts with DNA, damages the structure of the molecule. Currently, cisplatin is used in the treatment of numerous malignant neoplasms. Despite the high therapeutic efficacy, the drug has many side effects, which may include, among others: ototoxicity, cardiotoxicity, neurotoxicity, hepatotoxicity and nephrotoxicity. A significant problem in cisplatin therapy is also the development of resistance of cancer cells to the action of this drug. The mechanism of cell platinum resistance is diverse and depends on many factors. Organ toxicity and the development of resistance induced by cisplatin may limit the pharmacological dose of the drug and its therapeutic efficacy. Therefore, studies are still being conducted to assess the therapeutic effect of the combined interaction of cisplatin with other chemotherapeutic agents and compounds with anticancer potential.

Key words: cancer, chemotherapy, cisplatin, platinum resistance, toxicity, multi-drug therapy

Oncol Clin Pract 2022; 18, 3: 166–176

Introduction

Neoplastic diseases are still a serious health problem in the modern world. The main methods of fighting cancer are radiation therapy, immunotherapy, and hormone therapy. A common and frequently used method in the treatment of many types of cancer is chemotherapy, which provides the use of drugs with a broad effect. Drugs used in cancer chemotherapy constitute a diverse group of compounds. They include, among others, topoisomerase inhibitors (camptothecin derivatives, anthracyclines), microtubule stabilizers (taxanes, vinca alkaloids), antimetabolites (gemcitabine, methotrexate, 5-fluorouracil), and alkylating drugs (cyclophosphamide, ifosfamide) [1]. Chemotherapeutic agents containing metal atoms also play an important role in the treatment of cancer. The group of alkylating drugs includes platinum compounds, such as cisplatin, carboplatin, and oxaliplatin [1]. Currently, cisplatin is a platinum complex widely used in oncological therapy. Despite its high efficiency, this compound is highly toxic. Therefore, efforts are still made to develop new therapies based on using cisplatin in combination with other compounds with anti-cancer potential. Multi-drug treatment of neoplastic cells may increase therapeutic efficacy.

The issue of the mechanisms of the formation, growth, and treatment of neoplastic diseases is still discussed in numerous scientific papers. This study aims to present the mechanisms of the cellular interaction of cisplatin, the development of cellular resistance, the range of side effects, and new possibilities for using cisplatin in anticancer therapy.

Received: 17.02.2022 Accepted: 10.03.2022 Early publication date: 31.05.2022

Cisplatin

Historical overview

Cisplatin [cis-dichlorodiammine platinum (II)] is a first-generation platinum drug containing two chloride ligands in the *cis* configuration [2]. This compound was synthesized in 1845 by A. Werner, who 48 years later described the chemical structure of cisplatin. In the 1960s, a research team led by B. Rosenberg observed that cisplatin is formed as a result of the electrolysis of platinum electrodes [3]. By analyzing the effect of the electromagnetic field on bacterial cells, Rosenberg and his colleagues found that cisplatin inhibits the proliferation of bacterial cells [3, 4]. Therefore, there were indications that this compound may show an inhibitory effect on other cells, including cancer [3]. The antiproliferative effect of cisplatin on cancer cells was confirmed in an experimental mouse model [3, 5], which resulted in the implementation of cisplatin in subsequent research stages. Based on the results obtained, in 1978 cisplatin was approved as an anti-cancer drug [6]. However, studies were still conducted to assess the effectiveness of this drug in various types of cancer cells [7, 8].

Transport and biotransformation

The structure of cisplatin in the blood, due to the high concentration of chloride ions (approx. 100 mM), shows great stabilization [4]. This compound undergoes biological changes only after the drug is absorbed into the cell [9]. The process of cisplatin transport into cells has not been fully elucidated. Literature data show that cisplatin can penetrate the plasma membrane by passive diffusion [10, 11]. There are also reports that the partial uptake of cisplatin may be mediated by protein transporters [11]. Copper transporters (Ctr1, Ctr2), ATPase (ATP7A, ATP7B), organic cation transporters (OCT-2), and multidrug and toxin extrusion proteins (MATE 1) are probably associated with the transport of cisplatin through cytoplasmic membranes [11, 12]. Membrane transporters involved in the uptake and accumulation of cisplatin in cancer cells are responsible both for the effectiveness of the drug and the development of side effects [10]. Transport of cisplatin to cells can also take place with the participation of the sodium-potassium pump (Na^+/K^+-ATPase) [4].

Cisplatin is hydrolyzed inside the cell [4]. This process is regulated by the appropriate concentration of chloride ions. The reduced level of Cl^- ions in the intracellular environment (approx. 4-12 mM) accelerates the hydrolysis of cisplatin [9]. It has been shown that the positively charged molecules formed by hydrolysis ($cis\text{-}[Pt(NH_3)_2Cl_2(OH_2)]^+$/$cis\text{-}[Pt(NH_3)_2Cl_2(OH_2)_2]^{2+}$) are characterized by a higher biological activity than the neutral forms of the complex [13]. Therefore, it is believed that it is the secondary metabolite of cisplatin [cis-diaminadihydroxyplatin (II)] that exhibits strong pharmacotherapeutic properties [14].

The mechanism of antitumor action

Literature data show that the mechanism of the anti-cancer effect of cisplatin is based on the direct effect of the drug on the DNA structure. The basis of cisplatin's action is the creation of cross-links in the DNA structure between platinum (II) and two adjacent guanine molecules [15]. According to the literature, the most commonly observed is the attachment of cisplatin to the N7 atoms of guanine [9]. Presumably, the Pt-N7 guanine bonds formed in this way show high stability and thus determine the cytotoxic effect of the compound on cancer cells [16]. Cisplatin can cross-link with base pairs within a single strand or between a DNA double helix, resulting in the formation of monoadducts or diadducts (double adducts). The type of Pt-DNA adducts formed may exert a significant influence on the biological activity of the drug. It was found that the genotoxic effect of cisplatin results from the formation of monoadducts, while the formation of double adducts — inside or between strands — results in the cytotoxic properties of the compound [17]. Nevertheless, the resulting adducts lead to a disturbance of the spatial structure of DNA, which results in inhibition of acid replication and transcription [2, 9, 14, 18]. Under normal conditions, repair systems are involved in the repair of DNA damage, including Nucleotide Excision Repair excision repair (NER), homologous recombination (HR), and mismatch repair Mismatch Repair System (MMR) [4, 19]. In neoplastic cells, depending on their sensitivity and the concentration of cisplatin used, the mechanisms of the repair process are disrupted, which results in the induction of apoptotic death signals. Depending on the type of DNA damage caused by cisplatin, in tumor cells, Ataxia Telangiectasia Rad 3-Related (ATR) and Mitogen-Activated Protein Kinases (MAPK) are activated, which stimulate p53 proteins in the further pathway of the cellular response [20]. Moreover, independent of the phosphorylation of the ATR kinases, the action of cisplatin triggers the expression of the p73 nuclear protein in the cells. The accumulation of p73 is related to cisplatin-activated oncogenic tyrosine kinase c-Abl. The increased reactivity of the p53 and p73 proteins leads to the activation of further mechanisms involved in the induction of the apoptosis process [18]. Cisplatin affects the internal pathway of apoptotic death by stimulating the pro-apoptotic protein Bax, changing the permeability of the mitochondrial membrane, releasing cytochrome c, and activating the caspase cascade [18]. Permeabilization of the mitochondrial membrane caused by cisplatin may also result from the drug's influence on the production of free oxygen radicals (ROS) [21, 22].

The literature shows that cisplatin, depending on its concentration, can also induce necrotic cell death [23]. Research results indicate that pronecrotic cisplatin concentrations first activate the mechanisms of apoptotic death, which can be blocked at the level of effector caspases. Inhibition of caspase activity consequently causes cell necrosis [23, 24]. Mediators of cisplatin-induced necrotic death may also be calpains, TNF-α cytokines, and poly (ADP-ribose)-1 (PARP1) polymerase — factors related to the mechanism of nephrotoxic action of the drug [24, 25].

The antitumor properties of cisplatin are also demonstrated by its antiproliferative activity. The complex has been shown to exert a strong influence on the checkpoints of the cell cycle. In response to DNA damage, the cell is initially arrested in the S phase. However, further action of cisplatin leads to an inhibition of cyclin Cdc2 A activity, which ultimately results in cell division arrest in the G2/M phase [18, 20]. Ataxia Telangiectasia Mutated (ATM) kinases, activated by the action of cisplatin, are also involved in the inhibition of cell division [20].

Mechanisms of cell resistance

The response of cancer cells to the cytostatic drugs has a significant impact on the effectiveness of chemotherapeutic treatment. In cancer therapy, the development of cellular resistance is a frequently observed phenomenon [5]. Drug resistance occurs when cancer cells fail to undergo apoptosis at a clinically specified dose [26]. The platinum resistance that hinders the treatment of neoplasms may have features of both innate and acquired resistance [27]. According to the literature, the mechanisms involved in platinum resistance vary and may be caused by: (1) decreased drug absorption resulting in reduced intracellular accumulation, (2) increased inactivation of cisplatin, (3) impaired drug transport into cells, (4) accelerated removal of the drug from cells (efflux), (5) intensified repair of the resulting DNA damage, mainly associated with the activation of NER repair systems [4, 13, 18, 19, 20, 26]. The disturbed signal of apoptotic death also has a significant influence on the development of cellular resistance. Cancer cells with p53 dysfunction acquire resistance through disrupted mechanisms of the apoptotic pathway [27]. A similar effect is also shown by the overexpression of apoptosis inhibitors, e.g. survivin and factor X-linked Inhibitor of Apoptosis Protein (XIAP), which increase platinum resistance by lowering the activity of caspases [26]. Weakened cisplatin transport to neoplastic cells during chemotherapeutic treatment may be caused by functional changes in plasma membranes and membrane transporters [27]. It is believed that overexpression of CTR1 transporters increases the sensitivity of cancer cells to cisplatin, enhancing its cytotoxic activity [16]. Their impaired functioning may, therefore, play an important role in the development of cell resistance to cisplatin treatment. The protein transporters ATP7A and ATP7B are also involved in the formation of cellular resistance. Increased ATP7A expression is responsible for the decreased effect of cisplatin in cancer cells while ATP7B overexpression results in accelerated drug outflow from cells [11].

According to the literature, platinum resistance may be associated with the overexpression of glutathione transferase (GSTs) [28]. The enzyme is associated with the drug detoxification process, which leads to inactivation of cisplatin and reduced treatment effectiveness [14, 28]. Therefore, the use of GSTs inhibitors (e.g. ethacrynic acid) may increase the accumulation of cisplatin in platinum-resistant cells and significantly improve the therapeutic effect [28]. The intracellular concentration of glutathione (GSH) is also associated with the platinum resistance mechanism. Until recently, the role of GSH in the development of cellular resistance to cisplatin was ambiguous [4]. It is now known that high GSH levels may promote cellular resistance [29]. Metallothioneins (MT) act in a similar way, and by capturing cisplatin, they reduce the sensitivity of cells to the drug [14, 30]. The greatest importance in the resistance mechanisms is attributed to the metallothioneins MT1 and MT2 [4, 31] although the participation of other proteins from the MT group is also possible. As reported in the literature, cisplatin binds to cysteine-rich proteins, therefore, high concentrations of glutathione and metallothioneins in neoplastic cells may favor the development of acquired resistance [32].

The development of cellular resistance to cisplatin may also result from the overexpression of cyclooxygenase (COX) [33–35], characteristic of many types of malignant tumors, e.g. cancer of the esophagus, bladder, cervix and ovary [30]. It was shown that the applied COX-2 inhibitors, by inhibiting the expression of the anti-apoptotic protein Bcl-2, can effectively increase the pharmacological activity of cisplatin [30]. The COX inhibitors include e.g. non-steroidal anti-inflammatory drugs [36]. Cisplatin conjugates with COX-1, and COX-2 inhibitors (e.g. indomethacin and ibuprofen) accelerate drug transport into cells, increase cytotoxic activity, and inhibit the development of drug resistance [33]. It has been observed that celecoxib may also have a similar effect in osteosarcoma [36] and ovary cells [35], and NS-398 in non-small cell lung cancer [34]. These compounds enhance the anti-cancer effect of cisplatin and, depending on the PI3K/Akt signaling pathway, induce the apoptotic death process [34, 36]. The importance of COX in reducing drug resistance of cancer cells is poorly understood. Currently, the role of COX inhibitors does not affect routine clinical practice. However,

the results obtained so far suggest that the use of COX inhibitors may become the direction of further research as a new strategy in cancer treatment. It is possible that the combination of cisplatin with COX inhibitors may in the future contribute to the improvement of the effectiveness of the anti-cancer therapies [37].

In addition to biochemical and molecular factors, environmental factors also play an important role in the resistance of cancer cells to cisplatin, e.g. pH value. Cisplatin activity has been observed to be greatest at acidic pH. Increased pH reduces the binding of cisplatin with DNA, inhibits the formation of Pt-DNA adducts, and thus weakens the pharmacological effect of the drug [30]. The mechanisms responsible for the development of resistance of cancer cells to cisplatin are diverse [20]. This is a key research issue in overcoming platinum resistance by cancer cells.

Toxicity

Cisplatin is used in the treatment of various types of cancer, including cancer of the head and neck, lung, testes, prostate, ovaries, bladder, cervix, esophagus, breast, and stomach [12, 38, 39]. The use of cisplatin and its effectiveness in cancer therapy may be limited due to numerous side effects. The frequency of side effects depends on the used cisplatin dose, including the cumulative dose (Tab. 1). Literature data report that some compounds have a protective effect against cisplatin-induced toxicity. Currently, these compounds are not routinely used in conjunction with anti-cancer therapy. However, studies are still being conducted to assess the protective potential of some of these compounds, therefore, they may find wider applications in the future.

Ototoxicity

Changes in the hearing system may appear early in the treatment with cisplatin [40]. Hearing impairment caused by the action of cisplatin depends on the dose and duration of drug action, as well as the patient's age [41], and is more often observed in children than adults [40, 41]. Ototoxic disorders can manifest as earache and tinnitus, leading to partial hearing loss. Initially in the high-frequency range of sounds [40], then also including lower tones [42], including persistent and bilateral ototoxicity [40]. The mechanisms underlying the development of cisplatin-induced ototoxicity remain unclear. It is assumed that a key role in the pathogenesis of ototoxicity may be played by a disturbed antioxidant system, development of inflammatory processes, induction of apoptosis, and cellular autophagy [42]. The use of protective agents may limit the ototoxic effects of cisplatin [41, 43]. Among them, great hope is raised, by N-acetylcysteine, D-methionine, ebselen, amifostine, dexamethasone, and flunarizine [43]. In clinical trials, the evaluation of the otoprotective effect of sodium thiosulfate (Identifier: NCT04541355, Phase II; Identifier: NCT04262336, Phase I) and N-acetylcysteine (Identifier: NCT04291209, Phase I and II; Identifier: NCT02094625, Phase I) was implemented.

Cardiotoxicity

Disorders in the proper functioning of the cardiovascular system caused by cisplatin can be diverse and include, among others, myocardial fibrosis and inflammation, heart failure, hypertension, arrhythmia [44]. There are reports in the literature describing cases in which patients developed cardiac dysfunction or even myocardial infarction after treatment with cisplatin [45].

Table 1. The incidence of cisplatin-induced toxicity

Cisplatin-induced toxicity	Frequency of appearance
Ototoxicity	Hearing loss: 31% [102]
	Hearing impairment: 10–15% [102]
	Otological complaints during cisplatin treatment: 24% [103]
	Otological complaints following cisplatin treatment: 34% [103]
Cardiotoxicity	Bradycardia, tachycardia: often (≥ 1/100 to < 1/10 of patients) [102]
	Hypertension, myocardial infarction: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Neurotoxicity	Peripheral neuropathy: often (≥ 1/100 to < 1/10 of patients) [102]
	Brain dysfunction: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Hepatotoxicity	Liver dysfunction, elevated levels of aminotransferase: often (≥ 1/100 to < 1/10 of patients) [102]
	Reduced albumin levels in the blood: rarely (≥ 1/10000 to < 1/1000 of patients) [102]
Nephrotoxicity	Acute kidney injury: very often (≥ 1/10 of patients) [102]
	20–30% [39]
	28–42% [104]
	32% [105]

Cisplatin-induced cardiovascular disorders most often limit the continuation of chemotherapy [44]. The effect of cisplatin on cardiotoxicity remains unclear. Presumably, electrolyte imbalances, including hypomagnesemia caused by the action of cisplatin, may play a significant role in the development of cardiological changes [45]. Early diagnosis of cardiotoxicity can prevent permanent complications of the cardiac system [45]. Literature data report the cardioprotective effect of some agents against cisplatin-induced changes in animals, e.g. ginger [44], thymoquinone [46], green tea, vitamin E [47], acetyl L-carnitine [48].

Neurotoxicity

The development of the neurotoxic effect of cisplatin is determined by the accumulation of the drug in the dorsal root ganglia, which may affect the proper functioning of sensory neurons [49] and the development of peripheral neuropathy [50]. The changes in the nervous system may be permanent and may limit the range of therapeutic doses [50, 51]. Often, adverse effects of cisplatin on the nervous system may not appear until after chemotherapy has been completed [50]. The mechanism of the neurotoxic effect of cisplatin may be related to oxidative damage, mitochondrial dysfunction, inhibition of proliferation, and induction of apoptosis of neuronal cells [51, 52]. It has been shown that the neuroprotective factors in relation to changes induced by cisplatin include, *inter alia*, glutathione and vitamin E [53]. In experimental animal models, it has been observed that cisplatin-induced neurotoxicity can also be reduced by routin, which, by enhancing the antioxidant system, has a protective effect on brain tissue [51]. Literature data show that concerning cisplatin activity, neuroprotective effects are also shown by oxytocin [54], sitagliptin [55], mesna [56], sodium selenite [57], and the Ginkgo Biloba extract [52].

Hepatotoxicity

Literature data show that cisplatin causes an increase in biochemical indicators and changes in the structure of hepatocytes. Cisplatin-induced hepatotoxicity may result from increased drug accumulation in liver cells [58]. Although the mechanism of the toxic effect of cisplatin on the liver has not been fully understood, it is assumed that the development of hepatotoxicity is a result of increased oxidative stress [58, 59]. It has been observed in studies *in vitro* and *in vivo* that the hepatotoxic effect of cisplatin may be enhanced by elevated levels of cytochrome P 450 2E1 [59]. Mitochondrial disorders, increased lipid peroxidation, abnormal Ca^{2+} homeostasis, and increased expression of the pro-inflammatory factor COX-2 are the basic aspects of the adverse effect of cisplatin on the liver [58]. According to the literature data, the hepatotoxic effect of cisplatin can be minimized by using compounds with antioxidant activity [60–65] or anti-apoptotic [65]. It has been shown that liver damage caused by cisplatin can be alleviated by, among others, dexpanthenol [60], hyperin [61], licorice extract [62], propofol [63], curcumin, vitamin E [64], and vinpocetine [65].

Nephrotoxicity

The nephrotoxic effect of cisplatin is a significant clinical problem. It can develop in approximately 30% of patients treated with cisplatin [39, 66]. Most often it manifests itself in acute kidney damage. The development of nephrotoxicity is closely correlated with the dose and frequency of drug administration [39] and thus with the degree of cisplatin accumulation in renal tubular cells [67]. OCT2 protein transporters play an important role in the development of the nephrotoxic effect of cisplatin, increasing the drug uptake in kidney cells [67]. According to the literature, cisplatin may disturb renal vascularization and lead to damage to the proximal tubules, mainly due to the induction of oxidative stress and overexpression of pro-inflammatory factors [67]. In the pathomechanism of renal cell damage, an important role is also played by signaling pathways responsible for the processes of apoptotic and necrotic death, as well as autophagy and the cell cycle [66–68]. Regulation of these factors may both limit the nephrotoxicity of cisplatin and reduce its therapeutic potential [12]. Therefore, the search for new compounds with a protective effect against the nephrotoxic effect of cisplatin is still ongoing. It has been observed that gelsemin [38], cilastatin [69], saponins isolated from the leaves of *Panax quinquefolius* [70], quercetin [68], eriocitrin [71], and mannitol [72], among others, may show the nephroprotective effect. Phase II and III clinical trials are still ongoing to evaluate the protective effects of pantoprazole and rosuvastatin against cisplatin-induced nephrotoxicity (Identifier: NCT04217512, NCT04817904) [73].

The use of cisplatin in multi-drug therapy

Cisplatin is used both as monotherapy and in combination therapy. The effectiveness of new cisplatin-based treatment regimens is still the subject of numerous clinical trials. These studies aim to compare the therapeutic efficacy of cisplatin in multi-drug systems in different types of cancer (Tab. 2) [73].

Lung cancer

Cisplatin-based chemotherapy has become a breakthrough in the treatment of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). This chemotherapy is most effective in adjuvant and first-line treatment of NSCLC. It is also recommended to use two-drug systems with cisplatin and third-generation drugs. The standard chemothera-

Table 2. Sample clinical trials for the assessment of the effects of cisplatin in multi-drug therapy for selected malignant neoplasms (current status as of January 2022) [73]

Cancer	Combination Therapy	Drug (dose)	Clinical Trials Phase	Clinical Trials Identifier
Non-Small Cell Lung Cancer (NSCLC)	Cisplatin/Camrelizumab/ Paclitaxel	Cisplatin (75 mg/m^2), Camrelizumab (200 mg), Paclitaxel (130 mg/m^2)	II	NCT04338620$^{(R)}$
	Cisplatin/Gemcitabine	Cisplatin (60 mg), Gemcitabine (200 mg)	I	NCT02889666$^{(R)}$
	Cisplatin/Pemetrexed	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2)	III	NCT02743923$^{(ANR)}$
	Cisplatin/Pemetrexed	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2)	III	NCT02657434$^{(ANR)}$
	Cisplatin/Pemetrexed/Atezolizumab	Cisplatin (75 mg/m^2), Pemetrexed (500 mg/m^2), Atezolizumab (1200 mg)	III	NCT02657434$^{(ANR)}$
	Cisplatin/Etoposide	Cisplatin (80 mg/m^2), Etoposide (100 mg/m^2)	III	NCT02875457$^{(NR)}$
	Cisplatin/Etoposide/Apatinib	Cisplatin (80 mg/m^2), Etoposide(100 mg/m^2) Apatinib (250 mg/d)	III	NCT02875457$^{(NR)}$
Triple-Negative Breast Cancer (TNBC)	Nab-paclitaxel/Cisplatin/ /Carilizumab	Nab-Paclitaxel (125 mg/m^2), Cisplatin (75 mg/m^2), Carilizumab (200 mg)	II	NCT04537286$^{(R)}$
	Gemcitabine/Cisplatin	Gemcitabine (1250 mg/m^2), Cisplatin (75 mg/m^2)	II	NCT04297267$^{(R)}$
	Eribulin/Cisplatin *vs.* Gemcitabine/Cisplatin	Eribulin (1.4 mg/m^2), Cisplatin (75 mg/m^2) *vs.* Gemcitabine (1250 mg/m^2), Cisplatin (75 mg/m^2)	II	NCT04517292$^{(NR)}$
	Chidamine/Cisplatin	Chidamine (20 mg), Cisplatin (75 mg/m^2)	II	NCT04192903$^{(NR)}$
	Docetaxel/Cisplatin	Docetaxel (75 mg/m^2), Cisplatin (25 mg/m^2)	II	NCT04664972$^{(R)}$
Ovarian Cancer	Mitomycin C/Cisplatin	Mitomycin C (10 mg/m^2), Cisplatin (100 mg/m^2)	Not Applicable	NCT04747717$^{(R)}$
	Nab-paclitaxel/ Cisplatin/ /Sintilimab	Nab-paclitaxel (180-220 mg/m^2), Cisplatin (60-80 mg/m^2),Sintilimab (200 mg)	I/II	NCT03989336$^{(R)}$
	Manganese Chloride/Nab--paclitaxel/Cisplatin/Sintilimab	Manganese Chloride (0,4 mg/kg — inhalation), Nab-paclitaxel (180-220 mg/m^2), Cisplatin (60-80 mg/m^2), Sintilimab (200 mg)	I/II	NCT03989336$^{(R)}$
Bladder Cancer	Radiotherapy/Cisplatin	Radiotherapy (to 63 Gy), Cisplatin (20 mg/m^2)	Not Applicable	NCT01495676$^{(ANR)}$
	Radiotherapy/Cisplatin/ Gemcitabine	Radiotherapy (to 63 Gy), Cisplatin (20 mg/m^2), Gemcitabine (25 mg/m^2)	Not Applicable	NCT01495676$^{(ANR)}$
	Atezolizumab/Gemcitabine/ Cisplatin	Atezolizumab (1200 mg/m^2), Gemcitabine (1000 mg/m^2), Cisplatin (70 mg/m^2)	II	NCT03093922$^{(ANR)}$
	Etoposide/Cisplatin	Etoposide (100 mg/m^2), Cisplatin (80 mg/m^2)	II/III	NCT03992911$^{(R)}$
	Pembrolizumab/Cisplatin/ Gemcitabine	Pemrolizumab (200 mg), Cisplatin (35 mg/m^2), Gemcitabine (1000 mg/m^2)	II	NCT02690558$^{(ANR)}$
	Cabazitaxel/Cisplatin	Cabazitaxel (15 mg/m^2), Cisplatin (70 mg/m^2)	II	NCT01616875$^{(ANR)}$
Head and Neck Cancer	Cambrelizumab/Radiotherapy/ /Cisplatin	Cambrelizumab, Radiotherapy (66–70 Gy), Cisplatin (75–100 mg/m^2)	II	NCT04405154$^{(NR)}$
	Cambrelizumab/ /Cisplatin/Nab-paclitaxel	Cambrelizumab (200 mg), Cisplatin (60 mg/m^2), Nab-paclitaxel (260 mg/m^2)	II	NCT04826679$^{(R)}$
	Radiotherapy/Pembrolizumab/ /ISA101b/ Cisplatin	Radiotherapy (70 Gy), Pembrolizumab (200 mg), ISA101b, Cisplatin (100 mg/m^2)	II	NCT04369937$^{(R)}$
	Paclitaxel/Cisplatin *vs.* Docetaxel/Cisplatin	Paclitaxel (260 mg/m^2), Cisplatin (75 mg/m^2) *vs.* Docetaxel (75 mg/m^2), Cisplatin (75 mg/m^2)	IV	NCT04766827$^{(R)}$
Prostate Cancer	Pembrolizumab/Etoposide/ /Cisplatin	no data	I	NCT03582475$^{(R)}$
Testicular Cancer	Bleomycin/Etoposide/Cisplatin *vs.* Carboplatin	no data	III	NCT02341989$^{(ANR)}$
	Etoposide/Cisplatin/Radiation Therapy	Etoposide (100 mg/m^2), Cisplatin (20 mg/m^2), Radiotherapy (2 Gy — 3 weeks later)	II	NCT03937843$^{(R)}$

$^{(ANR)}$ — active, not recruting; $^{(NR)}$ — not yet recruiting; $^{(R)}$ — recruiting

peutic treatment regimen for NSCLC includes, *inter alia*, administration of cisplatin in combination with paclitaxel. The effective interaction of cisplatin with nab-paclitaxel in relation to advanced NSCLC cancer was reported by Hattori et al [74] in Phase I and II clinical trials. Hayashi et al. [75] suggested the possibility of concurrent use of cisplatin in combination with nab-paclitaxel and radiation therapy for the treatment of locally advanced NSCLC. When assessing the effectiveness of the therapy in Phase I/II clinical trials, it was shown that concurrent chemoradiotherapy in combination with cisplatin and nab-paclitaxel can be a promising method of treatment for NSCLC in patients under 75 years of age, with normal renal function [75]. There are still ongoing studies evaluating the effectiveness of cisplatin and paclitaxel with, among others, sintilimab (Identifier: NCT04840290), pemetrexed and tislelizumab (Identifier: NCT04379635) [73]. An alternative in the treatment of lung cancer is also the combined action of cisplatin with vinorelbine [76]. In contrast, in an experimental animal model, it has been shown that cisplatin in combination with erlotinib can be effective in inhibiting tumor growth in lung cancer [77]. Phase I clinical trials (Identifier: NCT04809103) are currently underway to determine the maximum dose of tolerated cisplatin administered bronchoscopically to the tumor in patients diagnosed with NSCLC [73].

Breast cancer

In the second phase of clinical trials, Rosati et al. [78] observed that in patients with metastatic breast cancer resistant to anthracyclines, a well-tolerated chemotherapy regimen may be a treatment based on the combination of cisplatin and paclitaxel. However, it has been shown that an adverse reaction resulting from the use of this therapy was increased neurotoxicity [78]. According to the literature data, the combined effect of cisplatin and gemcitabine may also be very effective in the treatment of breast cancer [79]. It was found that the combination of cisplatin with gemcitabine, despite the observed side effects [80], may have a beneficial therapeutic effect and constitute an alternative treatment for patients with triple-negative metastatic breast cancer (TNBC) [79, 80]. Similar conclusions were presented after the combined action of cisplatin with nab-paclitaxel [81]. High therapeutic activity and a mild toxic profile were obtained in Phase II clinical trials (Identifier: NCT01928680) as a result of TNBC treatment with cisplatin and capecitabine, initiated after initial treatment with anthracyclines and taxanes [73, 82].

Ovarian cancer

The use of cisplatin in the treatment of ovarian cancer has proved to be an important chemotherapy strategy. In the treatment of advanced ovarian cancer, the treatment regimen based on the use of cisplatin with paclitaxel [83] and cisplatin with cyclophosphamide [84] was also assessed. Phase III studies conducted by Mouratidou et al. [84] suggest a stronger response of ovarian cancer cells to cisplatin with paclitaxel therapy than to cisplatin with cyclophosphamide although with no clear differences in disease progression and survival time. In palliative chemotherapy, in the treatment of advanced or recurrent ovarian cancer, it has been observed that the combination of cisplatin and topotecan may be highly effective. However, this activity was associated with the unfavorable effect of the complexes on hematological indicators [85]. Hoskins et al. [86], in the assessment of Phase III clinical trials, did not observe significant changes in the pharmacological efficacy of the combined effect of cisplatin with topotecan in relation to carboplatin and paclitaxel therapy. Reports from literature data indicate that the use of cisplatin with doxorubicin may be beneficial in the treatment of ovarian cancer [87]. Moreover, in women with advanced and inoperable ovarian cancer, high efficacy was observed after combining cisplatin with doxorubicin in intraperitoneal negative pressure aerosol chemotherapy [87]. Phase II studies have also been implemented to evaluate the dosing regimen and pharmacodynamics of cisplatin used as intraperitoneal chemoperfusion in women with stage III epithelial ovarian cancer (Identifier: NCT02567253) [73].

Bladder cancer

First-line chemotherapy based on cisplatin is one of the basic treatments for advanced urothelial tumors [88]. In metastatic bladder cancer, standard cancer therapy includes methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC regimen) [89]. Literature data indicate that cisplatin and gemcitabine chemotherapy may also have a beneficial effect in the treatment of advanced bladder cancer [88]. This therapy is also used in neoadjuvant treatment [89]. The use of cisplatin with gemcitabine in induction chemotherapy has also been suggested in patients with invasive bladder cancer [90, 91] although the obtained results of Phase III clinical trials were inconclusive and called for further analyzes [90]. Okabe et al. [89] observed that cisplatin and gemcitabine cumulative treatment of infiltrating bladder cancer shows a therapeutic effect comparable to the MVAC regimen. In addition, treatment based on the combined effect of cisplatin with atezolizumab and pembrolizumab may gain recognition in the treatment of advanced and metastatic urothelial neoplasms [73].

Head and neck cancer

The standard topical treatment for advanced squamous cell neoplasms of the head and neck is cisplatin chemotherapy with radiotherapy [92]. Studies determin-

ing the dosing regimen of cisplatin used concurrently with radiotherapy are still ongoing [93, 94]. The efficacy of cisplatin in induction chemotherapy in advanced, inoperable head and neck cancer has also been observed in combination with 5-fluorouracil [95], as well as in a regimen with fluorouracil and docetaxel [92]. Yokota et al. [92] showed that in the treatment of head tumors, chemoradiotherapy initiated after previous induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (cisplatin was given in divided doses) may have a beneficial therapeutic effect and low toxicity. Moreover, Fietkau et al. [96], comparing chemoradiotherapy regimens in advanced head and neck cancer in Phase III clinical trials, found that a reduced dose of radiotherapy with concomitant cisplatin and paclitaxel has a therapeutic effect comparable to standard chemoradiotherapy, with cisplatin and fluorouracil.

Prostate and testicular cancer

Literature data indicate that first-line treatment of prostate cancer includes docetaxel therapy [97]. In Phase II clinical trials, it has been observed that, after prior docetaxel treatment, a beneficial therapeutic effect can be obtained after administration of cisplatin with prednisone [98]. Chemotherapy based on the combined action of cisplatin with gemcitabine may also be effective in the treatment of advanced prostate cancer [99]. Cisplatin-based therapy is also the standard treatment for testicular cancer. The use of cisplatin in the treatment of testicular cancer has contributed to the improvement of the therapeutic efficacy and an increase in the cure rate since the 1980s [100]. Currently, the standard treatment of testicular cancer includes the BEP regimen using cisplatin, etoposide, and bleomycin [101]. Phase III clinical trials are also conducted to compare the effectiveness of the multi-drug BEP regimen and the dose-dense combination chemotherapy containing cisplatin, etoposide, bleomycin, paclitaxel, oxaliplatin, and ifosfamide in patients with stage II or stage III non-seminomatous germ cell (Identifier: NCT00104676) [73].

Summary

The high efficacy of cisplatin in the treatment of malignant neoplasms may be limited by developing cellular resistance and numerous side effects. Currently, research is being conducted to find and implement new therapeutic strategies using cisplatin, also in combination with other chemotherapeutic agents and substances with potential anti-cancer properties. Perhaps the use of cisplatin in new multi-drug therapy regimens will contribute to increasing the effectiveness of oncological treatment.

Conflict of interest

Authors declare no conflict of interest.

References

1. Heinhuis KM, Ros W, Kok M, et al. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol. 2019; 30(2): 219–235, doi: 10.1093/annonc/mdy551, indexed in Pubmed: 30608567.
2. Aldossary S. Review on Pharmacology of Cisplatin: Clinical Use, Toxicity and Mechanism of Resistance of Cisplatin. Biomed Pharmacol J. 2019; 12(1): 07–15, doi: 10.13005/bpj/1608.
3. Florea AM, Büsselberg D. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers (Basel). 2011; 3(1): 1351–1371, doi: 10.3390/cancers3011351, indexed in Pubmed: 24212665.
4. Basu A, Krishnamurthy S. Cellular responses to Cisplatin-induced DNA damage. J Nucleic Acids. 2010; 2010, doi: 10.4061/2010/201367, indexed in Pubmed: 20811617.
5. Makovec T. Cisplatin and beyond: molecular mechanisms of action and drug resistance development in cancer chemotherapy. Radiol Oncol. 2019; 53(2): 148–158, doi: 10.2478/raon-2019-0018, indexed in Pubmed: 30956230.
6. Yeku O, Russo AL, Lee H, et al. A phase 2 study of combined chemo-immunotherapy with cisplatin-pembrolizumab and radiation for unresectable vulvar squamous cell carcinoma. J Transl Med. 2020; 18(1): 350, doi: 10.1186/s12967-020-02523-5, indexed in Pubmed: 32928237.
7. Kempf SR, Ivankovic S. Carcinogenic effect of cisplatin (cis-diammine-dichloroplatinum (II), CDDP) in BD IX rats. J Cancer Res Clin Oncol. 1986; 111(2): 133–136, doi: 10.1007/BF00400751, indexed in Pubmed: 3084495.
8. Moul J, Dodge R, Robertson J, et al. The impact of the ?cisplatin era? of treatment on survival in testicular cancer. World J Urol. 1991; 9(1), doi: 10.1007/bf00184714.
9. Browning RJ, Reardon PJ, Parhizkar M, et al. Drug Delivery Strategies for Platinum-Based Chemotherapy. ACS Nano. 2017; 11(9): 8560–8578, doi: 10.1021/acsnano.7b04092, indexed in Pubmed: 28829568.
10. Ciarimboli G. Membrane transporters as mediators of Cisplatin effects and side effects. Scientifica (Cairo). 2012; 2012: 473829, doi: 10.6064/2012/473829, indexed in Pubmed: 24278698.
11. Spreckelmeyer S, Orvig C, Casini A. Cellular transport mechanisms of cytotoxic metallodrugs: an overview beyond cisplatin. Molecules. 2014; 19(10): 15584–15610, doi: 10.3390/molecules191015584, indexed in Pubmed: 25268716.
12. Volarevic V, Djokovic B, Jankovic MG, et al. Molecular mechanisms of cisplatin-induced nephrotoxicity: a balance on the knife edge between renoprotection and tumor toxicity. J Biomed Sci. 2019; 26(1): 25, doi: 10.1186/s12929-019-0518-9, indexed in Pubmed: 30866950.
13. Zhou J, Kang Yu, Chen Lu, et al. The Drug-Resistance Mechanisms of Five Platinum-Based Antitumor Agents. Front Pharmacol. 2020; 11: 343, doi: 10.3389/fphar.2020.00343, indexed in Pubmed: 32265714.
14. Śliwińska-Hill U, Szumełda M. Biologiczne podstawy terapii przeciwnowotworowej z zastosowaniem leków platynowych. Oddziaływanie z cytochromem c. Nowotwory J Oncol. 2016; 66(2): 136–150, doi: 10.5603/njo.2016.0023.
15. Kozakiewicz K, Kaczmarczyk M. Cisplatin — a by-chance drug. Curr Gynecol Oncol. 2012; 10(2): 131–140.
16. Trynda-Lemiesz L, Śliwińska-Hill U. Kompleksy metali w terapii nowotworowej. Teraźniejszość i przyszłość. Nowotwory J Oncol. 2011; 61(5): 465–474.
17. Subocz M, Popławska B, Bielawska A, et al. Pochodne platyny w chemioterapii chorób nowotworowych. Annal Acad Med Siles. 2011; 65(4): 70–76.
18. Tanida S, Mizoshita T, Ozeki K, et al. Mechanisms of Cisplatin-Induced Apoptosis and of Cisplatin Sensitivity: Potential of BIN1 to Act as a Potent Predictor of Cisplatin Sensitivity in Gastric Cancer Treatment. Int J Surg Oncol. 2012; 2012: 862879, doi: 10.1155/2012/862879, indexed in Pubmed: 22778941.
19. Sun CY, Nie J, Huang JP, et al. Targeting STAT3 inhibition to reverse cisplatin resistance. Biomed Pharmacother. 2019; 117: 109135, doi: 10.1016/j.biopha.2019.109135, indexed in Pubmed: 31226634.

20. Galluzzi L, Senovilla L, Vitale I, et al. Molecular mechanisms of cisplatin resistance. Oncogene. 2012; 31(15): 1869–1883, doi: 10.1038/onc.2011.384, indexed in Pubmed: 21892204.
21. Choi YM, Kim HK, Shim W, et al. Mechanism of Cisplatin-Induced Cytotoxicity Is Correlated to Impaired Metabolism Due to Mitochondrial ROS Generation. PLoS One. 2015; 10(8): e0135083, doi: 10.1371/journal.pone.0135083, indexed in Pubmed: 26247588.
22. Kleih M, Böpple K, Dong M, et al. Direct impact of cisplatin on mitochondria induces ROS production that dictates cell fate of ovarian cancer cells. Cell Death Dis. 2019; 10(11): 851, doi: 10.1038/s41419-019-2081-4, indexed in Pubmed: 31699970.
23. Sancho-Martínez SM, Piedrafita FJ, Cannata-Andía JB, et al. Necrotic concentrations of cisplatin activate the apoptotic machinery but inhibit effector caspases and interfere with the execution of apoptosis. Toxicol Sci. 2011; 122(1): 73–85, doi: 10.1093/toxsci/kfr098, indexed in Pubmed: 21527773.
24. Dursun B, He Z, Somerset H, et al. Caspases and calpain are independent mediators of cisplatin-induced endothelial cell necrosis. Am J Physiol Renal Physiol. 2006; 291(3): F578–F587, doi: 10.1152/ajprenal.00455.2005, indexed in Pubmed: 16622172.
25. Park S, Yoon SP, Kim J. Cisplatin induces primary necrosis through poly(ADP-ribose) polymerase 1 activation in kidney proximal tubular cells. Anat Cell Biol. 2015; 48(1): 66–74, doi: 10.5115/acb.2015.48.1.66, indexed in Pubmed: 25806124.
26. Siddik ZH. Cisplatin: mode of cytotoxic action and molecular basis of resistance. Oncogene. 2003; 22(47): 7265–7279, doi: 10.1038/sj.onc.1206933, indexed in Pubmed: 14576837.
27. Weiss-Gradzińska W, Krzempek W, Trynda-Lemiesz L. Mechanizm oporności na leki platynowe oraz strategie pokonywania tego zjawiska. Wiad Chem. 2013; 67: 1105–1128.
28. Li S, Li C, Jin S, et al. Overcoming resistance to cisplatin by inhibition of glutathione S-transferases (GSTs) with ethacraplatin micelles in vitro and in vivo. Biomaterials. 2017; 144: 119–129, doi: 10.1016/j.biomaterials.2017.08.021, indexed in Pubmed: 28834763.
29. Han Yu, Yin W, Li J, et al. Intracellular glutathione-depleting polymeric micelles for cisplatin prodrug delivery to overcome cisplatin resistance of cancers. J Control Release. 2018; 273: 30–39, doi: 10.1016/j.jconrel.2018.01.019, indexed in Pubmed: 29371047.
30. Stewart DJ. Mechanisms of resistance to cisplatin and carboplatin. Crit Rev Oncol Hematol. 2007; 63(1): 12–31, doi: 10.1016/j.critrevonc.2007.02.001, indexed in Pubmed: 17336087.
31. Amable L. Cisplatin resistance and opportunities for precision medicine. Pharmacol Res. 2016; 106: 27–36, doi: 10.1016/j.phrs.2016.01.001, indexed in Pubmed: 26804248.
32. Lee JH, Chae JW, Kim JK, et al. Inhibition of cisplatin-resistance by RNA interference targeting metallothionein using reducible oligo--peptoplex. J Control Release. 2015; 215: 82–90, doi: 10.1016/j.jconrel.2015.07.015, indexed in Pubmed: 26210439.
33. Neumann W, Crews BC, Marnett LJ, et al. Conjugates of cisplatin and cyclooxygenase inhibitors as potent antitumor agents overcoming cisplatin resistance. ChemMedChem. 2014; 9(6): 1150–1153, doi: 10.1002/cmdc.201402074, indexed in Pubmed: 24801194.
34. Jiang GB, Fang HY, Tao DY, et al. COX-2 potentiates cisplatin resistance of non-small cell lung cancer cells by promoting EMT in an AKT signaling pathway-dependent manner. Eur Rev Med Pharmacol Sci. 2019; 23(9): 3838–3846, doi: 10.26355/eurrev_201905_17811, indexed in Pubmed: 31115011.
35. Deng L, Feng DQ, Ling B. Cyclooxygenase-2 promotes ovarian cancer cell migration and cisplatin resistance via regulating epithelial mesenchymal transition. J Zhejiang Univ Sci B. 2020; 21(4): 315–326, doi: 10.1631/jzus.B1900445, indexed in Pubmed: 32253841.
36. Liu B, Yan S, Qu L, et al. Celecoxib enhances anticancer effect of cisplatin and induces anoikis in osteosarcoma via PI3K/Akt pathway. Cancer Cell Int. 2017; 17: 1, doi: 10.1186/s12935-016-0378-2, indexed in Pubmed: 28053596.
37. Li S, Jiang M, Wang Lu, et al. Combined chemotherapy with cyclooxygenase-2 (COX-2) inhibitors in treating human cancers: Recent advancement. Biomed Pharmacother. 2020; 129: 110389, doi: 10.1016/j.biopha.2020.110389, indexed in Pubmed: 32540642.
38. Lin L, Zheng J, Zhu W, et al. Nephroprotective effect of gelsemine against cisplatin-induced toxicity is mediated via attenuation of oxidative stress. Cell Biochem Biophys. 2015; 71(2): 535–541, doi: 10.1007/s12013-014-0231-y, indexed in Pubmed: 25343941.
39. Miller RP, Tadagavadi RK, Ramesh G, et al. Mechanisms of Cisplatin nephrotoxicity. Toxins (Basel). 2010; 2(11): 2490–2518, doi: 10.3390/toxins2112490, indexed in Pubmed: 22069563.
40. Callejo A, Sedó-Cabezón L, Juan ID, et al. Cisplatin-Induced Ototoxicity: Effects, Mechanisms and Protection Strategies. Toxics. 2015; 3(3): 268–293, doi: 10.3390/toxics3030268, indexed in Pubmed: 29051464.
41. Sheth S, Mukherjea D, Rybak LP, et al. Mechanisms of Cisplatin-Induced Ototoxicity and Otoprotection. Front Cell Neurosci. 2017; 11: 338, doi: 10.3389/fncel.2017.00338, indexed in Pubmed: 29163050.
42. Yu D, Gu J, Chen Y, et al. Current Strategies to Combat Cisplatin-Induced Ototoxicity. Front Pharmacol. 2020; 11: 999, doi: 10.3389/fphar.2020.00999, indexed in Pubmed: 32719605.
43. Hazlitt RA, Min J, Zuo J. Progress in the Development of Preventative Drugs for Cisplatin-Induced Hearing Loss. J Med Chem. 2018; 61(13): 5512–5524, doi: 10.1021/acs.jmedchem.7b01653, indexed in Pubmed: 29361217.
44. El-Hawwary AA, Omar NM. The influence of ginger administration on cisplatin-induced cardiotoxicity in rat: Light and electron microscopic study. Acta Histochem. 2019; 121(5): 553–562, doi: 10.1016/j.acthis.2019.04.013, indexed in Pubmed: 31068261.
45. Sawant S, Prakruthi J, Daddi A, et al. Cisplatin-induced cardiotoxicity — two case reports. OncoReview. 2015; 5(4): 145–150, doi: 10.5604/20828691.1189719.
46. Adalı F, Gonul Y, Kocak A, et al. Effects of thymoquinone against cisplatin-induced cardiac injury in rats. Acta Cir Bras. 2016; 31(4): 271–277, doi: 10.1590/S0102-865020160040000008, indexed in Pubmed: 27168540.
47. Ibrahim MA, Bakhaat GA, Tammam HG, et al. Cardioprotective effect of green tea extract and vitamin E on Cisplatin-induced cardiotoxicity in mice: Toxicological, histological and immunohistochemical studies. Biomed Pharmacother. 2019; 113: 108731, doi: 10.1016/j.biopha.2019.108731, indexed in Pubmed: 30851549.
48. Bayrak S, Aktaş S, Altun Z, et al. Antioxidant effect of acetyl-l-carnitine against cisplatin-induced cardiotoxicity. J Int Med Res. 2020; 48(8): 300060520951393, doi: 10.1177/0300060520951393, indexed in Pubmed: 32865065.
49. Kanat O, Ertas H, Caner B. Platinum-induced neurotoxicity: A review of possible mechanisms. World J Clin Oncol. 2017; 8(4): 329–335, doi: 10.5306/wjco.v8.i4.329, indexed in Pubmed: 28848699.
50. von Schlippe M, Fowler CJ, Harland SJ. Cisplatin neurotoxicity in the treatment of metastatic germ cell tumour: time course and prognosis. Br J Cancer. 2001; 85(6): 823–826, doi: 10.1054/bjoc.2001.2006, indexed in Pubmed: 11556831.
51. Almutairi MM, Alanazi WA, Alshammari MA, et al. Neuro-protective effect of rutin against Cisplatin-induced neurotoxic rat model. BMC Complement Altern Med. 2017; 17(1): 472, doi: 10.1186/s12906-017-1976-9, indexed in Pubmed: 28962559.
52. Gomaa DH, Hozayen WG, Al-shafeey H, et al. Ginkgo biloba Alleviates Cisplatin-Mediated Neurotoxicity in Rats via Modulating APP/A /P2X7R/P2Y12R and XIAP/BDNF-Dependent Caspase-3 Apoptotic Pathway. Applied Sciences. 2020; 10(14): 4786, doi: 10.3390/app10144786.
53. Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemother Res Pract. 2011; 2011: 843019, doi: 10.1155/2011/843019, indexed in Pubmed: 22312559.
54. Akman T, Akman L, Erbas O, et al. The preventive effect of oxytocin to Cisplatin-induced neurotoxicity: an experimental rat model. Biomed Res Int. 2015; 2015: 167235, doi: 10.1155/2015/167235, indexed in Pubmed: 25688351.
55. Li Y, Zheng M, Sah SK, et al. Neuroprotective influence of sitagliptin against cisplatin-induced neurotoxicity, biochemical and behavioral alterations in Wistar rats. Mol Cell Biochem. 2019; 455(1-2): 91–97, doi: 10.1007/s11010-018-3472-z, indexed in Pubmed: 30446906.
56. Saadati H, Noroozzadeh S, Esmaeili H, et al. The Neuroprotective Effect of Mesna on Cisplatin-Induced Neurotoxicity: Behavioral, Electrophysiological, and Molecular Studies. Neurotox Res. 2021; 39(3): 826–840, doi: 10.1007/s12640-020-00315-9, indexed in Pubmed: 33216283.
57. Karavelioglu E, Boyaci MG, Simsek N, et al. Selenium protects cerebral cells by cisplatin induced neurotoxicity. Acta Cir Bras. 2015; 30(6): 394–400, doi: 10.1590/S0102-865020150060000004, indexed in Pubmed: 26108027.
58. Mir M, Arab MR, Shahraki MR, et al. Toxic Effects of Cisplatin on Hepatocytes and Liver Enzymes of Rats. ASJ. 2015; 12(4): 171–176.
59. Lu Y, Cederbaum AI. Cisplatin-induced hepatotoxicity is enhanced by elevated expression of cytochrome P450 2E1. Toxicol Sci. 2006; 89(2): 515–523, doi: 10.1093/toxsci/kfj031, indexed in Pubmed: 16251482.
60. Bilgic Y, Akbulut S, Aksungur Z, et al. Protective effect of dexpanthenol against cisplatin-induced hepatotoxicity. Exp Ther Med. 2018; 16(5): 4049–4057, doi: 10.3892/etm.2018.6683, indexed in Pubmed: 30402149.
61. Niu C, Ma M, Han X, et al. Hyperin protects against cisplatin-induced liver injury in mice. Acta Cir Bras. 2017; 32(8): 633–640, doi: 10.1590/s0102-865020170080000005, indexed in Pubmed: 28902939.
62. Man Q, Deng Yi, Li P, et al. Licorice Ameliorates Cisplatin-Induced Hepatotoxicity Through Antiapoptosis, Antioxidative Stress, Anti-In-

flammation, and Acceleration of Metabolism. Front Pharmacol. 2020; 11: 563750, doi: 10.3389/fphar.2020.563750, indexed in Pubmed: 33240085.
63. Akram R, Ghazal S, Tayebeh S, et al. Hepatoprotective Effects of Propofol in Cisplatin Induced Rat Liver Oxidative Damage. Pharmacologia. 2016; 7(4): 229–233, doi: 10.5567/pharmacologia.2016.229.233.
64. Palipoch S, Punsawad C, Koomhin P, et al. Hepatoprotective effect of curcumin and alpha-tocopherol against cisplatin-induced oxidative stress. BMC Complement Altern Med. 2014; 14: 111, doi: 10.1186/1472-6882-14-111, indexed in Pubmed: 24674233.
65. Habib SA, Abdelrahman RS, Abdel Rahim M, et al. Anti-apoptotic effect of vinpocetine on cisplatin-induced hepatotoxicity in mice: The role of Annexin-V, Caspase-3, and Bax. J Biochem Mol Toxicol. 2020; 34(10): e22555, doi: 10.1002/jbt.22555, indexed in Pubmed: 32578916.
66. Higuchi K, Yanagawa T. Evaluating dose of cisplatin responsible for causing nephrotoxicity. PLoS One. 2019; 14(4): e0215757, doi: 10.1371/journal.pone.0215757, indexed in Pubmed: 31022233.
67. Ruggiero A, Ariano A, Triarico S, et al. Cisplatin-induced nephrotoxicity in children: what is the best protective strategy? J Oncol Pharm Pract. 2021; 27(1): 180–186, doi: 10.1177/1078155220961550, indexed in Pubmed: 32990190.
68. Casanova AG, Prieto M, Colino CI, et al. A Micellar Formulation of Quercetin Prevents Cisplatin Nephrotoxicity. Int J Mol Sci. 2021; 22(2), doi: 10.3390/ijms22020729, indexed in Pubmed: 33450917.
69. Humanes B, Camaño S, Lara JM, et al. Cisplatin-induced renal inflammation is ameliorated by cilastatin nephroprotection. Nephrol Dial Transplant. 2017; 32(10): 1645–1655, doi: 10.1093/ndt/gfx005, indexed in Pubmed: 28340076.
70. Ma ZN, Li YZ, Li W, et al. Nephroprotective Effects of Saponins from Leaves of Panax quinquefolius against Cisplatin-Induced Acute Kidney Injury. Int J Mol Sci. 2017; 18(7), doi: 10.3390/ijms18071407, indexed in Pubmed: 28703736.
71. Jing Y, Wu X, Jiang H, et al. Nephroprotective effects of eriocitrin via alleviation of oxidative stress and DNA damage against cisplatin-induced renal toxicity. Turk J Biochem. 2020; 45(4): 381–388, doi: 10.1515/tjb-2019-0399.
72. Hägerström E, Lindberg L, Bentzen J, et al. The Nephroprotective Effect of Mannitol in Head and Neck Cancer Patients Receiving Cisplatin Therapy. Clin Med Insights Oncol. 2019; 13: 1179554918821320, doi: 10.1177/1179554918821320, indexed in Pubmed: 30670924.
73. www.clinicaltrials.gov.
74. Hattori Y, Kono Y, Itoh S, et al. A phase I/II study of weekly nab-paclitaxel plus cisplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer. BMC Cancer. 2020; 20(1): 115, doi: 10.1186/s12885-020-6588-y, indexed in Pubmed: 32046667.
75. Hayashi H, Ogura M, Niwa T, et al. Phase I/II Study of Cisplatin plus Nab-Paclitaxel with Concurrent Thoracic Radiotherapy for Patients with Locally Advanced Non-Small Cell Lung Cancer. Oncologist. 2021; 26(1): 19–e52, doi: 10.1002/ONCO.13524, indexed in Pubmed: 32918791.
76. Palka M, Sanchez A, Córdoba M, et al. Cisplatin plus vinorelbine as induction treatment in stage IIIA non-small cell lung cancer. Oncol Lett. 2017; 13(3): 1647–1654, doi: 10.3892/ol.2017.5620, indexed in Pubmed: 28454304.
77. Zhang Xu, Chen J, Jin H, et al. Effect of erlotinib combined with cisplatin on IL-6 and IL-12 in mice with Lewis lung cancer. Oncol Lett. 2020; 20(1): 902–906, doi: 10.3892/ol.2020.11632, indexed in Pubmed: 32566018.
78. Rosati G, Riccardi F, Tucci A, et al. A Phase II Study of Paclitaxel/Cisplatin Combination in Patients with Metastatic Breast Cancer Refractory to Anthracycline-Based Chemotherapy. Tumori Journal. 2018; 86(3): 207–210, doi: 10.1177/030089160008600306.
79. Koshy N, Quispe D, Shi R, et al. Cisplatin-gemcitabine therapy in metastatic breast cancer: Improved outcome in triple negative breast cancer patients compared to non-triple negative patients. Breast. 2010; 19(3): 246–248, doi: 10.1016/j.breast.2010.02.003, indexed in Pubmed: 20227277.
80. Hu XC, Zhang J, Xu BH, et al. Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. The Lancet Oncology. 2015; 16(4): 436–446, doi: 10.1016/s1470-2045(15)70064-1.
81. Li Yi, Zhao Y, Gong C, et al. Cisplatin shows greater efficacy than gemcitabine when combined with nab-paclitaxel in metastatic triple-negative breast cancer. Sci Rep. 2019; 9(1): 3563, doi: 10.1038/s41598-019-39314-y, indexed in Pubmed: 30837503.
82. Li Q, Li Q, Zhang P, et al. A phase II study of capecitabine plus cisplatin in metastatic triple-negative breast cancer patients pretreated with anthracyclines and taxanes. Cancer Biol Ther. 2015; 16(12): 1746–1753, doi: 10.1080/15384047.2015.1095400, indexed in Pubmed: 26466918.
83. Sugiyama T, Yakushiji M, Aoki Y, et al. Paclitaxel-cisplatin combination in advanced ovarian cancer: a phase II study. International Journal of Clinical Oncology. 2000; 5(2): 85–88, doi: 10.1007/s101470050096.
84. Mouratidou D, Gennatas C, Michalaki V, et al. A phase III randomized study comparing paclitaxel and cisplatin versus cyclophosphamide and cisplatin in patients with advanced ovarian cancer. Anticancer Res. 2007; 27(1B): 681–685, indexed in Pubmed: 17348460.
85. Lee MW, Ryu H, Song IC, et al. Efficacy of cisplatin combined with topotecan in patients with advanced or recurrent ovarian cancer as second- or higher-line palliative chemotherapy. Medicine (Baltimore). 2020; 99(17): e19931, doi: 10.1097/MD.0000000000019931, indexed in Pubmed: 32332673.
86. Hoskins P, Vergote I, Cervantes A, et al. Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel. J Natl Cancer Inst. 2010; 102(20): 1547–1556, doi: 10.1093/jnci/djq362, indexed in Pubmed: 20937992.
87. Tempfer CB, Giger-Pabst U, Seebacher V, et al. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018; 150(1): 23–30, doi: 10.1016/j.ygyno.2018.05.001, indexed in Pubmed: 29743140.
88. Furubayashi N, Negishi T, Takamatsu D, et al. Timing of changing therapy from gemcitabine and cisplatin chemotherapy based on real-world data of advanced urothelial carcinoma. Oncol Lett. 2020; 19(4): 2943–2949, doi: 10.3892/ol.2020.11368, indexed in Pubmed: 32256805.
89. Okabe Ko, Shindo T, Maehana T, et al. Neoadjuvant chemotherapy with gemcitabine and cisplatin for muscle-invasive bladder cancer: multicenter retrospective study. Jpn J Clin Oncol. 2018; 48(10): 934–941, doi: 10.1093/jjco/hyy122, indexed in Pubmed: 30169681.
90. Cognetti F, Ruggeri EM, Felici A, et al. Study Group(†). Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized phase III trial. Ann Oncol. 2012; 23(3): 695–700, doi: 10.1093/annonc/mdr354, indexed in Pubmed: 21859900.
91. Goel S, Sinha RJ, Bhaskar V, et al. Role of gemcitabine and cisplatin as neoadjuvant chemotherapy in muscle invasive bladder cancer: Experience over the last decade. Asian J Urol. 2019; 6(3): 222–229, doi: 10.1016/j.ajur.2018.06.006, indexed in Pubmed: 31297313.
92. Yokota T, Shibata M, Hamauchi S, et al. Feasibility and efficacy of chemoradiotherapy with concurrent split-dose cisplatin after induction chemotherapy with docetaxel/cisplatin/5-fluorouracil for locally advanced head and neck cancer. Mol Clin Oncol. 2020; 13(4): 35, doi: 10.3892/mco.2020.2105, indexed in Pubmed: 32802331.
93. Le X, Hanna EY. Optimal regimen of cisplatin in squamous cell carcinoma of head and neck yet to be determined. Ann Transl Med. 2018; 6(11): 229, doi: 10.21037/atm.2018.05.10, indexed in Pubmed: 30023392.
94. Helfenstein S, Riesterer O, Meier UR, et al. 3-weekly or weekly cisplatin concurrently with radiotherapy for patients with squamous cell carcinoma of the head and neck - a multicentre, retrospective analysis. Radiat Oncol. 2019; 14(1): 32, doi: 10.1186/s13014-019-1235-y, indexed in Pubmed: 30744643.
95. Rao R, Ss S, Shenoy V, et al. Induction Chemotherapy with Cisplatin and 5-Fluorouracil in Advanced Head and Neck Cancers: A Short Term Response Evaluation. J Clin Diagn Res. 2015; 9(10): XC08–XC12, doi: 10.7860/JCDR/2015/12191.6671, indexed in Pubmed: 26557601.
96. Fietkau R, Hecht M, Hofner B, et al. PacCis-Study Group. Randomized phase-III-trial of concurrent chemoradiation for locally advanced head and neck cancer comparing dose reduced radiotherapy with paclitaxel/cisplatin to standard radiotherapy with fluorouracil/cisplatin: The PacCis-trial. Radiother Oncol. 2020; 144: 209–217, doi: 10.1016/j.radonc.2020.01.016, indexed in Pubmed: 32044419.
97. Puente J, Grande E, Medina A, et al. Docetaxel in prostate cancer: a familiar face as the new standard in a hormone-sensitive setting. Ther Adv Med Oncol. 2017; 9(5): 307–318, doi: 10.1177/1758834017692779, indexed in Pubmed: 28529548.
98. Buonerba C, Federico P, D'Aniello C, et al. Phase II trial of cisplatin plus prednisone in docetaxel-refractory castration-resistant prostate cancer patients. Cancer Chemother Pharmacol. 2011; 67(6): 1455–1461, doi: 10.1007/s00280-011-1594-z, indexed in Pubmed: 21365219.

99. Kamiyama Y, Mitsuzuka K, Watanabe M, et al. Chemotherapy with Gemcitabine and Cisplatin for Advanced Ductal Adenocarcinoma of the Prostate: Clinical Courses of Two Patients. Tohoku J Exp Med. 2015; 237(4): 317–321, doi: 10.1620/tjem.237.317, indexed in Pubmed: 26633178.
100. de Vries G, Rosas-Plaza X, van Vugt MA, et al. Testicular cancer: Determinants of cisplatin sensitivity and novel therapeutic opportunities. Cancer Treat Rev. 2020; 88: 102054, doi: 10.1016/j.ctrv.2020.102054, indexed in Pubmed: 32593915.
101. Witkoś A, Copija A, Nowakowska-Zajdel E. Radical chemotherapy of massively disseminated testicular cancer in a 24-year-old patient with acute renal failure and cancer cachexia — case report. Oncol Clin Pract. 2017; 13(3): 138–140, doi: 10.5603/OCP.2017.0016.
102. Pałaszewska-Tkacz A, Świdwińska-Gajewska A, Czerczak S. Cisplatin. Documentation of proposed values of occupational exposure limits (OELs). Podstawy i Metody Oceny Środowiska Pracy. 2018; 34(1(95)): 13–52, doi: 10.5604/01.3001.0011.5845.
103. Santucci NM, Garber B, Ivory R, et al. Insight into the current practice of ototoxicity monitoring during cisplatin therapy. J Otolaryngol Head Neck Surg. 2021; 50(1): 19, doi: 10.1186/s40463-021-00506-0, indexed in Pubmed: 33766142.
104. Kou W, Qin H, Hanif S, et al. Nephrotoxicity Evaluation on Cisplatin Combined with 5-HT Receptor Antagonists: A Retrospective Study. Biomed Res Int. 2018; 2018: 1024324, doi: 10.1155/2018/1024324, indexed in Pubmed: 29977907.
105. Kidera Y, Kawakami H, Sakiyama T, et al. Risk factors for cisplatin-induced nephrotoxicity and potential of magnesium supplementation for renal protection. PLoS One. 2014; 9(7): e101902, doi: 10.1371/journal.pone.0101902, indexed in Pubmed: 25020203.

VIA MEDICA

REVIEW ARTICLE

Paweł M. Potocki, Piotr J. Wysocki

Oncology Department, Jagiellonian University Medical College, Cracow, Poland

Evolution of prostate cancer therapy. Part 1

Address for correspondence:
Lek. Paweł Potocki
Oncology Department,
Jagiellonian University Medical College
ul. Jakubowskiego 2, 30–688 Cracow, Poland
Tel. +48 12 4247275
e-mail: pawel.potocki@uj.edu.pl

Oncology in Clinical Practice
Translation: dr n. med. Dariusz Stencel
DOI: 10.5603/OCP. 2021.0001

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Prostate cancer is the most common cancer in men. Strategies relying on androgen deprivation have long been utilized in it's treatment. However, the therapy of castration-resistant disease still remains challenging. Therapeu-tic options have rapidly evolved during the last decade. New molecules with unprecedented activity, provided significant survival benefit in advanced disease. This review presents the key aspects of prostate cancer systemic therapy evolution over the last decades. The first part focuses on therapies active in castration-resistant disease. Part two reviews data on earlier therapy lines and principles relevant to devising optimal treatment sequence.

Key words: prostate cancer, castration-resistant, mCRPC, abiraterone, apalutamide, enzalutamide

Oncol Clin Pract 2022; 18, 3: 177–188

Introduction

In 1853, British surgeon John Adams described in the *Lancet* a case of a cirrhotic prostate gland with associated pelvic and lumbar lymphadenopathy. This case report is cited as the first-ever prostate cancer description [1]. Although Adams believed that the described disease was very rare, nowadays prostate cancer is the most common malignant tumour among men. In 2018, overall 1.28 million new cases were reported, and 0.38 million men died from the disease [2].

The relation between castration and secondary sexual characteristics has been known since antiquity. The scientific description of the effect of castration on prostate volume in animals was first published by James William White in 1893 [3]. In 1935, at intervals of several months, three researchers: Ernst Laqueur, Adolf Butenandt and Lavoslav Ružička, independently described the chemical structure of testosterone, initiating work on its role in mammalian physiology. In 1939, Butenandt and Ružička were awarded the Nobel Prize for their discovery. In 1941, Charles Huggins and Clarence Hodges jointly described the beneficial effects of surgical castration and oestrogen therapy on the course of metastatic prostate cancer [4]. Huggins continued his research in this area over the years, paving the way to modern systemic therapy of this cancer, for which he was also awarded the Nobel Prize in 1966. In 1969, Mainwaring et al. [5] discovered the androgen receptor (AR), which soon led to the description of its first inhibitor — cyproterone. In 1971, Andrew Schally described the structure and function of the gonadotropin-releasing hormone (GnRH) and its importance for the regulation of sex hormones [6]. In 1973–1976, long-acting analogues of this hormone were discovered, which were already registered as medicinal products in 1984–1987. During the next decade, further AR antagonists emerged with a more favourable therapeutic index.

The pathogenesis of prostate cancer is inextricably linked with AR. The management of pathological hormonal stimulation, as well as the mechanisms of cancer cell resistance to ADT, is the key to effective cancer therapy. Therapeutic options have therefore evolved from surgical through pharmacological castration to pharmaceuticals designed to counteract the molecular mechanisms that determine the development of castration resistance.

In this two-part review, the authors summarize the course of this evolution. They present the results of

Received: 28.12.2020 Accepted: 28.12.2020 Early publication date: 30.03.2022

ground-breaking research and indicate the most important, in the authors' opinion, directions for the further development of systemic treatment of patients with prostate cancer. The first part discusses the mechanisms of action of key drug classes and the data on their efficacy in metastatic, castration-resistant prostate cancer. Systemic treatment options in patients with castration-sensitive metastatic prostate cancer and patients with non-metastatic, castration-resistant cancer are presented in the second part, while discussing methods of optimizing sequential pharmacotherapy. It is in hope that it will allow the reader to better understand the landscape of available therapeutic options and the direction in which it is evolving, as well as facilitate decision-making in clinical practice.

Androgens and prostate cancer

Similarly to healthy prostate acinar and ductal cells, prostate cancer cells in untreated patients almost always express AR. It is a cytoplasmic protein, coded on the X chromosome and composed of several domains, including ligand-binding domain (LBD) and DNA binding domain (DBD). The inactive AR forms a complex with heat shock proteins (HSPs) 40, 70 and 90, which stabilize the receptor and prevent its proteolysis. Lipophilic androgens diffuse relatively easily across the cell membrane where they bind to the AR. This results in a two-time change in the receptor conformation and unbinding of HSP. This is followed by AR nuclear translocation mediated by the microtubular cytoskeleton. The AR displaced into the nucleus undergo homodimerization catalysed by nuclear coactivators, which leads to obtaining transcriptional activity by such a dimer, which in turn stimulates numerous genes promoters. AR activity determines the activation of several key mechanisms contributing to the carcinogenesis of prostate cancer and some other malignancies. This increases the proliferative drive, stimulates the secretory function, and neoangiogenesis (Fig. 1).

The androgens production in the male body is regulated by the activity of the hypothalamic-pituitary-gonadal (HPG) axis. Pulsatile changes of GnRH level in the hypothalamic-pituitary circulation cause the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). LH stimulates testosterone production by the Leydig cells of the testes, and FSH increases the production of plasma androgen binding protein (ABP). Androstenedione and dehydroepiandrosterone (DHEA) produced in adrenal glands, accounting for 10% of circulating androgens indicate a lower binding affinity for AR than testosterone. Their production, however, does not depend on the hormonal activity of the gonadal stimulating axis, but takes place constitutively, as it were, together with glucocorticosteroids synthesis. The androgen with the strongest affinity for AR is dihydrotestosterone (DHT), which is formed in the tissues: either from testosterone by the action of 5α-reductase (5AR) or from DHEA by the action of 17-hydroxylase/17.20-lyase (CYP17A1). There are two subtypes of the 5AR: the first is less active but is commonly present in various androgen-sensitive tissues, the second is more active, almost exclusively present in the prostate, making this organ extremely sensitive to androgen activity [7, 8].

The primary therapeutic approach in prostate cancer is androgen deprivation, which can be achieved in several ways. Bilateral orchiectomy or suppression of LH production by the pituitary gland can shut down testicular hormone production. Long-acting GnRH analogs (leuprorelin, goserelin, triptorelin) disrupt the natural rhythmic pattern of pulsatile GnRH secretion. In the initial phase, they cause the release of FSH and LH from the pituitary gland, which in turn causes an increase in testosterone concentration (the so-called flare-up phenomenon), but the final outcome is a durable HPG axis blockade. In turn, GnRH antagonists (abarelix, degarelix and oral relugolix) immediately inhibit the secretion of gonadotropic hormones, which prevents the flare-up effect. Other strategies of hormone therapy include substances that competitively block AR (bicalutamide, flutamide, nilutamide), antagonize its activity (oestrogens), and inhibit the conversion of androgens to DHT (finasteride, dutasteride, epristeride) (Tab. 1).

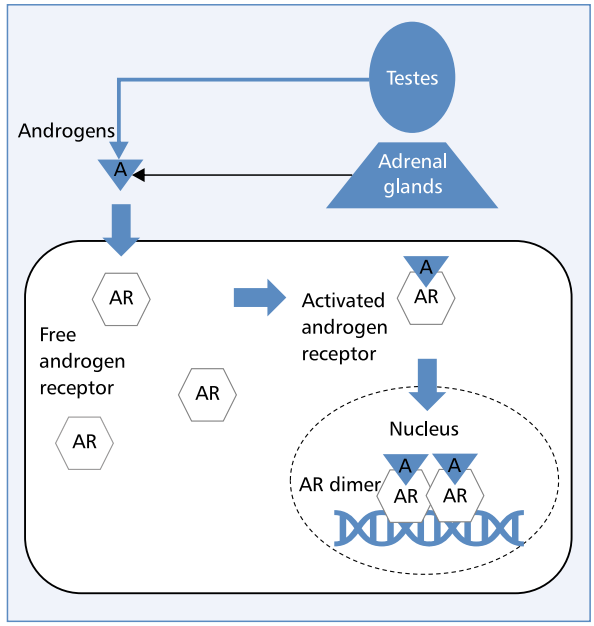

Figure 1. Androgen receptor-dependent signalling in a castration-sensitive prostate cancer cell; A — androgens; AR — androgen receptor

Table 1. Strategies affecting AR-dependent signalling pathways

Blocking androgen synthesis in the testes	Leuprorelin Goserelin Triptorelin Abarelix Degarelix Relugolix
Blocking androgens production in the adrenal glands	Glucocorticosteroids Adrenalectomy
Blocking enzymes responsible for androgen synthesis (adrenal, paracrine, autocrine)	Abiraterone Acetate Ketoconazole Aminoglutethimide
Blocking androgen conversion	Finasteride Dutasteride Epristeride
Reversing the androgen effect	Oestrogens
Inhibiting the binding of androgens to the receptor	Bicalutamide Flutamide Nilutamide Cyproterone Acetate Spironolactone
Multi-point blocking of androgen receptor activity	Enzalutamide Darolutamide Apalutamide
Blocking AR translocation	Docetaxel Cabazitaxel

Castration-resistant prostate cancer

The classic anti-androgen therapies described above have been and are successfully used in the treatment of patients with advanced prostate cancer. However, it should be remembered that in the case of prostate cancer, as with any other advanced neoplasms exposed to the long-term hormone therapy, there is always a loss of sensitivity to previously active hormone therapy. Historically, this condition was called hormone resistance, but today it is already known that at this stage of the disease, AR is still active and strongly promotes the progression of the neoplastic process. Thus, a more precise term has become widespread: castration-resistant prostate cancer (CRPC). The definition of castration resistance includes the occurrence of PSA increase and/or imaging progression during the effective castration confirmed by the testosterone level < 50 ng/dL (1.7 nmol/L). Most patients suffer from metastatic cancer at the time of resistance occurrence, but castration resistance can also be determined based on an increased PSA level alone without evidence of image progression. To meet the non-metastatic CRPC definition adopted by most societies, PSA increase must meet 3 conditions simultaneously: 1. three consecutive PSA increases separated by at least one week; 2. two increased values must be at least 50% higher than the nadir; 3. nominal PSA value must be > 2 ng/mL.

Knowing the molecular phenomena that determine castration resistance it is necessary to understand the mechanisms of action of drugs active for CRPC. First, as previously mentioned, the adrenal glands consistently produce small amounts of androgens in castrated patients. Additionally, in cancer cells or the tumour microenvironment, ectopic androgen production may occur. Moreover, the AR itself may be amplified, overexpressed, or activated by first-generation anti-androgen drugs. There may also be AR variants with increased affinity for the ligand or with constitutive, ligand-independent activity at all, arising from mutation or alternative AR DNA splicing. AR activity may also increase as a result of receptor phosphorylation by kinases associated with AR-independent signal transduction pathways from membrane receptors or as a result of increased expression of nuclear coactivators [9] (Fig. 2).

Therapies effective in overcoming castration resistance include cytotoxic drugs from the taxoid group; new generation anti-androgens that prevent the functioning of typical resistance mechanisms (apalutamide, darolutamide, enzalutamide, abiraterone acetate); radiopharmaceutical — radium-223; more recently PARP inhibitors (PARPi); and finally immunotherapeutics, of which, so far, only specific, active immunotherapy based on dendritic cells has proven effectiveness.

Chemotherapy

Until the end of the 20th century, no drugs were available to improve the prognosis of patients with CRPC. In the 1990s, strategies for prolonging progression-free survival emerged — those were estramustine, mitoxantrone or inhibition of adrenal androgen production with glucocorticosteroids.

The first drug that significantly improved the prognosis of patients with metastatic CRPC (mCRPC) was docetaxel — a synthetic derivative of paclitaxel, obtained from the tissues of European yew. Docetaxel was first described in the 1980s. Its mechanism of action, as in the case of other taxoids, is to stabilize microtubules by binding to β-subunit of tubulin [10]. The resulting dysfunction of the karyokinetic spindle is considered to be the main mechanism of action of taxoids. There are also data indicating additional mechanisms: inhibition of oncogenic kinases from the *BCL* family and disruption of activated AR nuclear translocation mediated by the microtubular cytoskeleton [11]. In 2000–2002, overall 1,006 men with mCRPC were enrolled in TAX-327 study [12, 13]. Patients were randomized in a 1:1:1 ratio to the group receiving: mitoxantrone (12 mg/m^2 q3w), docetaxel

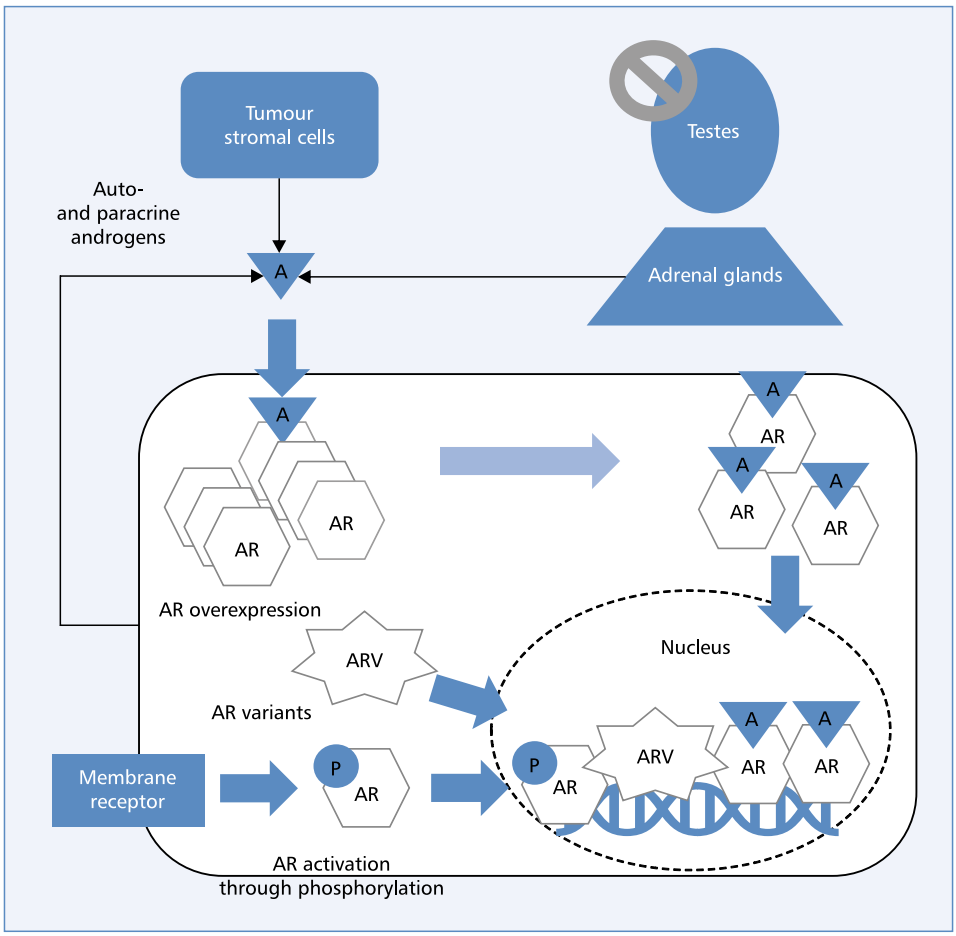

Figure 2. Mechanisms of castration resistance in the prostate cancer cell; A — androgens; AR — androgen receptor; ARV — AR variants

(75 mg/m^2 q3w) or docetaxel (30 mg/m^2 q1w). All patients also received a suppressive dose of prednisone (5 mg bid). The high dose docetaxel arm compared with the control arm showed a significant reduction in the relative risk of death by 21% [hazard ratio (HR) 0.79; 95% confidence interval (CI): 0.67–0.93; p = 0.004] with median overall survival (OS) of 19.2 months and 16.3 months, respectively. A low dose of weekly docetaxel was not associated with a significant prognosis improvement (median OS 17.8 months). Both PFS, objective response rate (ORR) and quality of life parameters were more favourable in patients receiving high dose docetaxel. Docetaxel was associated with a higher risk of neutropenia (32% *vs.* 22%), but not with febrile neutropenia or other cytopenias. Docetaxel also caused more gastrointestinal symptoms as well as neurotoxicity and skin toxicity, with a lower risk of hepatotoxicity than mitoxantrone. Subgroup analyses showed that patients who benefited most from the therapy were asymptomatic or with low symptoms intensity [The Functional Assessment of Cancer Therapy-Prostate (FACT-P) < 109], with no pain, in good performance status (PS) (KPS ≥ 90%), with no visceral metastases and high PSA levels (≥ 115 ng/mL). It can therefore be concluded that docetaxel-based therapy is best initiated in the early stages of mCRPC.

Cabazitaxel, first described in 1999, is a taxoid with a chemical structure and mechanism of action analogous to docetaxel. It has been designed to bypass the typical resistance mechanisms to classic taxanes that appear in cancer cells exposed to paclitaxel or docetaxel. In particular, cabazitaxel has no affinity for P-glycoprotein — a protein with transmembrane transporter activity — that actively removes xenobiotics (including docetaxel) from inside the tumour cell [14]. In 2010, the results of a phase III TROPIC study [15] were published, which assessed the effectiveness of cabazitaxel in mCRPC patients after failure of docetaxel treatment. In this study, 755 patients were randomized in a 1:1 ratio to either 25 mg/m^2 cabazitaxel or 12 mg/m^2 mitoxantrone, with both arms receiving a suppressive dose of prednisone. The study met its primary endpoint: it showed a significant reduction in the relative risk of death by 30% (HR = 0.70 95% CI: 0.59–0.83; p = 0.0001) with a median OS of 15.1 months (cabazitaxel) *vs.* 12.7 months

(mitoxantrone). Treatment in the experimental arm was clearly more toxic compared to the control arm. Adverse reactions were reported in 94% and 88% of patients, respectively, and CTCAE Grade ≥ 3 adverse events (AEs) in 82% and 58% patients in cabazitaxel and mitoxantrone arm, respectively.

It was widely believed that the development of new antiandrogens (discussed later) would diminish the position of cabazitaxel in a multi-step treatment strategy in mCRPC patients. It turns out, however, that this drug remains effective in subsequent lines of treatment. In September 2019, Ronald de Wit et al. [16] published in the NEJM the results of a phase IV CARD study [17], including 255 mCRPC patients who failed treatment with docetaxel and one of the new antiandrogens (abiraterone acetate or enzalutamide) used in any sequence. Patients were randomized in a 1:1 ratio to the cabazitaxel arm (25 mg/m^2 q3w) in combination with prednisone or the arm with a new generation of a previously unused hormonal drug (enzalutamide 160 mg/day or abiraterone acetate 1000 mg/day). The primary endpoint was radiological progression-free survival (rPFS). The secondary endpoints included, among others: OS, time to occurrence of skeletal events, and quality of life parameters.

The study met its primary endpoint. The median rPFS was 8.0 months for cabazitaxel and 3.7 months for the next-generation hormonal drug (HR = 0.54; 95% CI: 0.40–0.73; p < 0.001). The benefit of cabazitaxel was observed in all subgroups defined in the study, and in particular, no dependence of the activity of this drug on the previously used hormonal drug (enzalutamide *vs.* abiraterone) was demonstrated. The median OS was 13.6 months in the cabazitaxel arm and 11.0 months in the control arm, which translated into a significant reduction in the relative risk of death by 36% (HR = 0.64; 95% CI, 0.46–0.89; p < 0.008). After progression, 23.3% of patients in the active arm received a previously unused new anti-androgen in the subsequent treatment line. Cabazitaxel in the subsequent line was received by 33.3% of patients from the control arm. Of the patients with measurable lesions at randomization, an objective response was achieved by 37% of patients in the cabazitaxel arm and 12% patients in the hormone therapy arm (p = 0.004). The toxicity profile was consistent with data from previous studies.

Androgen synthesis inhibitors

Research on the pharmacological suppression of adrenal androgen production has been continued since at least the 1960s when aminoglutethimide was discovered — a pleiotropic drug, blocking, inter alia, CYP11A1 — the key enzyme for the conversion of cholesterol into steroid hormones precursors (Fig. 3). Aminoglutethimide effectively blocks the production of all steroid hormones, including glucocorticoid and mineralocorticoids, which in combination with its activity in other metabolic pathways, is responsible for its relatively high toxicity. In 2003–2007, ketoconazole (an antifungal imidazole derivative) activity was demonstrated in CRPC. This drug inhibits CYP11A1 and CYP17A — enzymes that block the conversion of gestagens to androgens. Suboptimal hormonal activity and the unfavourable safety profile of ketoconazole prevented the widespread use of this drug in clinical practice.

A milestone in the field of androgen synthesis inhibition was the introduction of second-generation anti-androgens, the first of which is abiraterone acetate, first described in 1995. While still not fully selective, by acting mainly by inhibiting CYP17A, it blocks the production of androgen precursors with a secondary induction of mineralocorticoids overproduction. Abiraterone is also a 5AR inhibitor, with glucocorticoid synthesis blocking effect, most likely dependent on CYP11B inhibition. Thus, during the use of abiraterone, glucocorticosteroids supplementation is necessary to prevent acute adrenal insufficiency (Fig. 3).

In the COU-AA-301 study, recruiting in 2008–2009, overall 1,195 mCRPC patients after treatment failure on docetaxel were randomized in a 2:1 ratio to prednisone treatment (5 mg bid) in combination with abiraterone acetate (1000 mg qd) or placebo. In August 2012, in "The Lancet" journal, Karim Fizazi et al. [18] published the final results of the COU-AA-301 study, showing a significant improvement in the prognosis of patients receiving abiraterone. The use of abiraterone reduced the relative risk of death compared to placebo by 26% (HR 0.74; 95% CI: 0.64–0.86; p = 0.0001) with a median OS of 15.8 *vs.* 11.2 months, respectively. Abiraterone benefits were also observed for other endpoints. The toxicity profile was favourable, and most adverse reactions, including those leading to treatment modification or discontinuation, occurred at similar rates in both arms. Adverse events more commonly observed in the active arm included fluid retention, oedema, hypokalaemia and urinary tract infections. The risk of hepatotoxicity did not differ significantly between the arms.

In 2013, Charles Ryan et al. [19, 20] published in the "NEJM" the results of the COU-AA-302 study, which investigated the efficacy of abiraterone in a population of asymptomatic or oligosymptomatic mCRPC patients without prior docetaxel treatment. Between 2009 and 2010, overall 1,088 patients were randomized to the abiraterone plus prednisone arm or the prednisone plus placebo arm. The co-primary endpoints were PFS and OS. Median OS differed significantly in favour of abiraterone: 34.7 months *vs.* 30.7 months, which translated into a 19% reduction in the relative risk of death

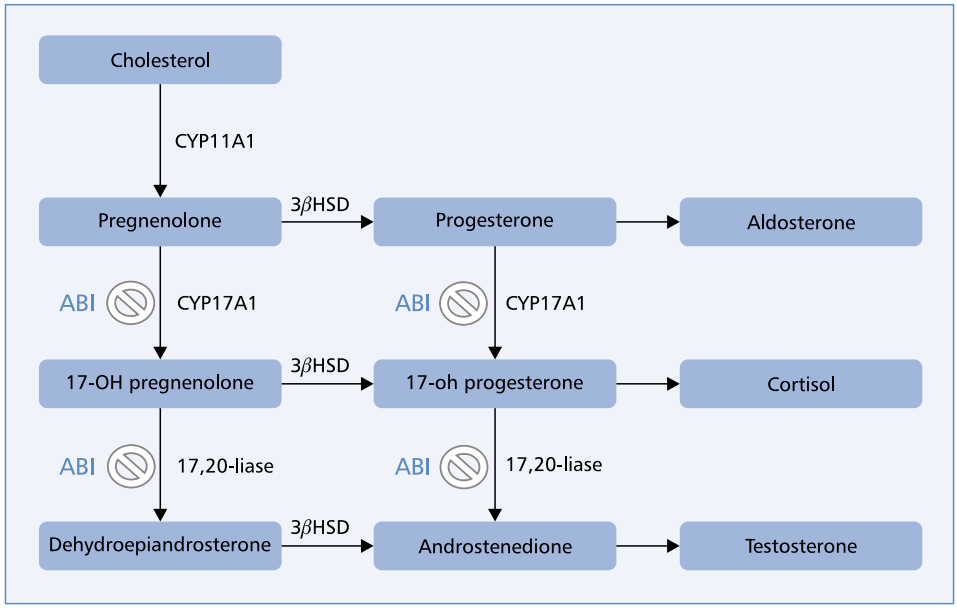

Figure 3. A simplified diagram of steroid hormone synthesis. Abiraterone mechanism of action

(HR = 0.81; 95% CI: 0.70–0.93; p = 0.0033). In the case of PFS [21], there was also a significantly higher median in the abiraterone arm — 16.5 months *vs.* 8.2 months (HR = 0.53; 95% CI: 0.45–0.61; p = 0.0001). More cardiovascular events, hepatotoxicity and hypertension were observed in the active arm.

Since 2012, enzalutamide (described in the next chapter) has been introduced in the indications analogous to those for abiraterone acetate. Although there is some competition between both medications, some researchers saw the potential in their combined use, due to the different mechanism of action.

At the American Society of Clinical Oncology (ASCO) 2018 Annual Meeting, Gerhardt Attard et al. [22] presented the results of the PLATO study, assessing the effectiveness of abiraterone in overcoming resistance to enzalutamide in a population of mCRPC patients who had not previously received chemotherapy with docetaxel. In the first step of the study, all patients received enzalutamide. Patients with primary resistance to this drug, as manifested by increased PSA level before the 21st week of therapy, were excluded from the study. The remaining patients at the time of PSA progression passed to stage II and were randomized in a 1:1 ratio to abiraterone in combination with enzalutamide or placebo. Therapy was continued until radiological progression or unacceptable toxicity. The primary endpoint was PFS. Of the 509 enrolled patients, 251 passed to the second stage (the reminded patients experienced no progression or did not meet the inclusion criteria). Median PFS did not differ significantly between the arms and was 5.7 months for the combination *vs.* 5.6 months for abiraterone monotherapy. There were no significant differences between other endpoints (including ORR). Combination therapy was associated with a higher risk of side effects (especially hypertension and hepatotoxicity).

At the ASCO 2019 Annual Meeting, Michael J. Morris et al. [23] presented the results of the phase III Alliance A031201 study, assessing the value of the combination of abiraterone and enzalutamide in the first-line mCRPC treatment. Prior treatment at the stage of castration sensitivity was allowed, including the early use of docetaxel. Patients included in the study were randomized in a 1:1 ratio to the combination of enzalutamide and abiraterone (+ prednisone) or enzalutamide monotherapy. Androgen deprivation was maintained in both groups. The primary endpoint was OS and the secondary endpoint was rPFS and biochemical response. From January 2014 to August 2016, overall 1,311 men were included in the study. There were no significant differences in OS: the median OS for the active and control arm was 32.7 months and 33.6 months, respectively, with combination therapy being more toxic.

New generation androgen receptor inhibitors

Enzalutamide, discovered in 2009, does not show partial agonist activity and binds the receptor more tightly than 1st generation AR inhibitors, reducing receptor affinity not only for its ligands. It also inhibits receptor nuclear translocation and the binding of AR to dimerization cofactors and DNA. The disadvantage of enzalutamide is the ability to penetrate the central nervous system and antagonize the receptors for

γ-aminobutyric acid (GABA) there, which can lead to neurological symptoms, in particular seizures.

In 2012, Howard Scher et al. [24] published in the "NEJM" the results of the phase III AFFIRM study, which assessed the effectiveness of enzalutamide in the treatment of mCRPC patients with imaging and/or biochemical progression after docetaxel therapy. In 2009–2010, overall 1,199 patients were randomized in a 2:1 ratio to treatment with enzalutamide at 160 mg/day or placebo. The study was terminated prematurely due to meeting its primary (OS) and secondary endpoints in the interim analysis. The median OS was 18.4 months (enzalutamide) and 13.6 months (placebo), respectively, which translated into a 37% reduction in the relative risk of death (HR = 0.63; 95% CI: 0.53–0.75; p = 0.001). The median rPFS was 8.3 months *vs.* 2.9 months in the experimental and control arm, respectively (HR = 0.25; p < 0.001); and radiological objective response rate was 29% *vs.* 4%, respectively. The overall incidence of adverse events did not differ significantly between the arms, and grade 3–4 toxicities were more frequent in the comparator arm. Seizures were observed only in the active arm, but only in 5 patients (0.6%).

In 2014, Tomasz Beer et al. [25] published in the "NEJM" the results of phase III PREVAIL study, assessing the effectiveness of enzalutamide in the treatment of mCRPC patients who had not been previously treated with docetaxel. In 2010–2012, overall 1,717 patients were randomized to enzalutamide 160 mg/day or placebo arm. The co-primary endpoints were PFS and OS. The study was terminated prematurely due to the proof of the test hypothesis in a stepwise analysis which showed an 81% reduction in the risk of disease progression or death and a 29% reduction in the risk of death in the enzalutamide arm. In the updated analysis presented in 2017 [26], the median PFS in the enzalutamide or placebo arms was 20.0 months and 5.4 months, respectively (HR = 0.32; 95% CI: 0.28–0.36; p < 0.0001), and median OS — 35.3 months and 31.3 months (HR = 0.77 95% CI: 0.67–0.88; p = 0.0002). In terms of the remaining endpoints, the superiority of the intervention was also demonstrated. The toxicity profile was comparable to the AFFIRM study, and enzalutamide was more commonly associated with fatigue, bone pain and diarrhoea, andropause symptoms, hypertension, and falls. Seizures were seen in one patient in each arm.

The advantage of enzalutamide over 1st generation antiandrogens was demonstrated in a randomized phase II STRIVE study, published in 2016. In this study, 396 patients with newly diagnosed CRPC (including 35% of patients without metastases) were randomized to the experimental arm with enzalutamide 160 mg/d or control arm with bicalutamide. For the primary endpoint (PFS — biochemical or radiological), a significant 76% reduction in relative risk was demonstrated, with a median PFS of 19.4 months (enzalutamide) *vs.* 5.7 months (bicalutamide) (HR = 0.24, 95% CI: 0.18–0.32; p = 0.001). For rPFS, a significant reduction in the risk of progression or death was also demonstrated with HR = 0.32 (95% CI: 0.21–0.50; p = 0.001), and a median of 5.7 months (bicalutamide) and not achieved in the enzalutamide arm.

Discovered in 2012, apalutamide is another next-generation anti-androgen with chemical and pharmacological properties similar to enzalutamide. This drug is characterized by a longer half-life, higher affinity for AR and lower permeability to CNS. The safety and activity of apalutamide were assessed in a phase I/II study (ARN-509-001) recruiting patients with mCRPC regardless of the number of prior systemic treatment lines. The results published in 2016 [27] indicated a comparable activity of apalutamide to enzalutamide.

Darolutamide is the newest, registered, second-generation anti-androgen with mechanisms of action analogous to those of apalutamide and enzalutamide. In contrast, however, darolutamide has antagonistic activity against some AR variants generated by mutations in the *AR* gene, making resistance development more difficult. Moreover, darolutamide is characterized by the strongest affinity for AR and the lowest CNS penetration compared to apalutamide and enzalutamide. The safety and activity of darolutamide were assessed in a phase I/II study (ARADES) including mCRPC patients in all treatment lines. The results of the study published in 2017 [28] confirmed that the activity of this drug is comparable to that of enzalutamide and apalutamide.

No further studies have been conducted with apalutamide and darolutamide in the treatment of mCRPC. Studies assessing the effectiveness of these drugs in the earlier stage of the disease will be presented in the second part of this review.

Radiopharmaceuticals

In the 1980s, systemic radiopharmaceuticals expanded the treatment armamentarium. Strontium-89, samarium-153, rhenium-186 and rhenium-188 emit mainly β-radiation with a tissue beam range of about 3 mm. The last three isotopes are also the source of gamma quanta, with an energy order of magnitude smaller, but with many times greater beam range. All of them have been shown to be effective in the treatment of bone metastases in the course of various cancers, but the benefit of their use is limited to symptoms alleviation (mainly pain intensity), without affecting the prognosis. The dose-limiting toxicity of all the above-mentioned radiopharmaceuticals is myelosuppression.

The desired characteristics of the isotope, which is to deliver a therapeutic dose of radiation in the area

of tumour bone remodelling, were defined relatively quickly. The uptake by the skeleton should be selective to avoid systemic toxicity and should have an optimal half-life: long enough to ensure a practical shelf life for the isotope, yet short enough to minimize dose retention and radiation safety related problems. Additionally, radioactive decay of the optimal radioisotope should be associated with emission of mainly α and β radiation, the low range of which in the tissues allows limiting myelotoxicity. Minimizing the emission of γ radiation significantly reduces the risk of systemic toxicity and eliminates problems related to radiological protection of people from the patient's surroundings. α radiation, due to the ease of energy transfer to molecules in tissues and causing mainly DNA double-stranded breaks (DSBs, is also much more effective in inducing cell death. It is estimated that already 1–4 "hits" on cellular DNA by the α particle are lethal for the cell, while in the case of β radiation nearly 1000 "hits" is needed [29].

Radium-223 was discovered in 1905 by Tadeusz Godlewski [30], a chemist associated with the Jagiellonian University. However, the anticancer potential of this isotope was only noticed at the end of the 20th century. All radium isotopes are calcimimetics — their electron shell mimics that of the calcium atom. Thus, both elements are characterized by a similar distribution in the body's tissues. After intravenous administration, radium is deposited primarily in the skeleton, showing a particularly high affinity for areas with the intense remodelling of the mineral matrix. Radioactive decay of radium-223 is associated almost exclusively with the emission of α radiation, with a small participation of β-decay (Fig. 4). The mechanism of action of the drug is primarily based on damaging the cancer cells DNA, but there are also data showing that it also modulates bone turnover, through toxic effects on osteoblasts and osteoclasts [31].

In 2013, Christopher Parker et al. [32, 33] published in the "NEJM" the results of the phase III ALSYMPCA study, which evaluated the effectiveness of radium-223 in the treatment of mCRPC patients with at least two symptomatic skeletal metastases. Participants could not have visceral or nodal metastases greater than 3 cm. In the case of patients without contraindications to the use of docetaxel, prior therapy with this drug was necessary. In 2008–2011, the study included 921 patients who were randomized in a 2:1 ratio to 6 doses of radium-223 (50 kBq/kg q4w) or placebo. After disease progression, patients in the placebo arm could receive radioisotope therapy. The primary endpoint of the study was OS and the secondary endpoints were time to first symptomatic skeletal-related event (SRE), time to PSA progression, and time to alkaline phosphatase progression. Radium treatment was associated with a significant reduction in the relative risk of death by 30% compared with placebo, with a median OS of 14.9 months (Radium-223) and 11.3 months (placebo) — HR = 0.70 (95% CI: 0.58–0.83; p = 0.001). The median time to SRE onset was 15.6 months (Radium-223) and 9.8 months (placebo); HR = 0.66 (95% CI: 0.52–0.83; p = 0.001). Additionally, a significant benefit of the use of Radium-223 was demonstrated in relation to the risk of PSA progression (HR = 0.64 95% CI: 0.54–0.77; p = 0.001) and alkaline phosphatase (HR = 0.17; 95% CI: 0.13–0.22; p = 0.001). In a subgroup analysis, the number of metastases ≥ 6 and the baseline alkaline phosphatase ≥ 200 U/L appeared to identify the patients who benefited most from the use of radioisotope. The incidence of adverse events, including serious and fatal ones, was slightly lower in the experimental arm. The most common side effects were cytopenia, bone pain, fatigue, nausea, and diarrhoea. There were no significant differences in the incidence of late complications in the long-term follow-up population. In 2013, Radium-223 was granted FDA and EMA marketing authorization for the treatment of docetaxel-resistant mCRPC patients.

There are numerous phase III studies ongoing to assess combinations of radium-223 with new anti-androgens, immunotherapy and other drugs. The final results of any of them have not been published yet, but an interesting observation has been published by the team conducting the ERA223 study. This study recruited mCRPC patients with at least two symptomatic skeletal metastases. Participants were not allowed to have visceral metastases or to receive prior docetaxel, radium-223, or abiraterone. All patients enrolled in the study received abiraterone in combination with prednisone and were randomized in a 1: 1 ratio to the Radium-223 arm or placebo. The study did not meet the primary endpoint (time to SRE). The median time to SRE was shorter in the radium-223 arm (22.3 months) compared to the placebo arm (26.0 months) — HR 1.122 (95% CI: 0.917–1.374; p = 0.2636). Secondary endpoints also indicated an adverse effect of the combination of radium and abiraterone. Based on retro-

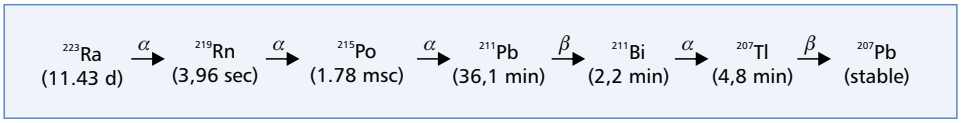

Figure 4. Radium-223 decay chain. Types of decay above the arrows, half-lives in brackets

spective analyses, it was hypothesized that the adverse therapeutic effect was associated with the lower use of bone turnover modulators in the Radium-223 arm compared to placebo. However, while pending further clarification of this finding, the EMA and the FDA have issued warning notices regarding simultaneous use of abiraterone and radium-223.

Immunotherapy

In the middle of the first decade of the 21st century, the American company Dendreon introduced a dendritic vaccine — sipuleucel-T. This medicinal product consists of autologous peripheral blood mononuclear cells (including dendritic cells) incubated with a recombinant antigen resulting from the fusion of the prostate acid phosphatase gene with the granulocyte colony-stimulating factor (G-CSF) gene. In 2006, Eric Small et al. [34] published in the *JCO* the results of phase III D9901 study, which compared sipuleucel-T (administered every 2 weeks) with placebo. The study recruited patients with asymptomatic mCRPC with a baseline Gleason score ≤ 6. The primary endpoint was time to progression (TTP) radiological or clinical (pain or SRE). Patients who progressed in the placebo arm could receive sipuleucel-T. The study did not meet its primary endpoint: the HR for progression-free survival was 1.45 (95% CI: 0.99–2.11; p = 0.052), with a median TTP of 11.7 weeks (vaccine) *vs.* 10.0 weeks (placebo). However, there was a significantly higher risk of death in the placebo arm (HR = 1.70 95% CI: 1.13–2.56; p = 0.01), with a median OS of 25.9 months (sipuleucel-T) *vs.* 21.4 months (placebo). The benefit in terms of OS was maintained in the multivariate analysis, however, the D9901 study was not designed to show a difference in overall survival [30]. In another phase III IMPACT study, the primary endpoint was OS. In the years 2003–2007, overall 512 mCRPC patients were enrolled in this study, regardless of the initial grade or symptoms intensity. Patients were randomized in a 2:1 ratio to either the vaccine or placebo arm. In 2010, Philip Kantoff et al. [35] published in the *NEJM* the results indicating a significantly higher risk of death in the placebo arm (HR = 1.78; 95% CI: 0.61–0.98; p = 0.03) with a median OS of 25.8 months (vaccine) *vs.* 21.7 months (placebo). The benefit of immunotherapy was reaffirmed in a multivariate analysis. Again, no significant differences were found in progression-free survival, which, as we know today, is typical for drugs stimulating specific, cellular antitumor response.

Although antibodies targeting immune checkpoints (CTLA4 as well as PD-1 and PD-L1) have been registered in over 60 indications since 2011, they have not yet been used in prostate cancer. Ipilimumab (an anti-CTLA4 antibody) showed promising activity in phase II trials, however, in a phase III study, no improvement in the prognosis of mCRPC patients was shown [36, 37]. Pembrolizumab, nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) showed varying degrees of activity in Phase I and II trials, and all of these ICIs are currently being intensively studied in this indication. The results of the studies conducted so far favour combinations rather than monotherapy. However, none of the phase III studies conducted so far has shown a significant improvement in the prognosis of patients after the use of immune checkpoint inhibitors. The main reasons for this include low tumour immunogenicity and the immunosuppressive effect of its stroma.

In November 2019, Emmanuel Antonarakis et al. [38] published in the *JCO* the results of a multi-cohort phase II Keynote-199 study. The study recruited mCRPC patients who received 2–3 lines of prior systemic treatment containing docetaxel and a new generation anti-androgen. In 2016–2017, overall 133 patients with measurable disease showing PD-L1 expression were included in cohort 1, 133 patients with measurable disease but no PD-L1 expression to cohort 2, and 59 patients with the predominance of bone lesions, regardless of PD-L1 expression to cohort 3. All patients received pembrolizumab (200 mg IV q3w up to a maximum of 35 cycles). The primary endpoint was the ORR in cohorts 1 and 2 (RECIST 1.1). ORR in patients with the measurable disease according to RECIST 1.1 criteria (cohorts 1 and 2) was 5%, with complete responses in two patients in cohort 1. The disease control rate in all cohorts according to RECIST 1.1 criteria was 12%, the highest (22%) in cohort 3. The biochemical response rate (PSA decrease by more than 50%) in the entire study population was 6%. Responses were durable: the median duration of response in the overall population was 16.8 months (the highest in cohort 1 — median not reached). Median rPFS was 2.1 months; 2.1 months and 3.7 months, and median OS: 9.5 months (95% CI 6.4–11.9 months); 7.9 months (95% CI 5.9–10.2 months) and 14.1 months (95% CI 10.8–17.6 months) in cohorts 1, 2, and 3, respectively.

Cabozantinib is a pleiotropic multi-kinase inhibitor with anti-angiogenic, anti-proliferative and anti-resorptive effects. It seems to be a promising partner for immunotherapy because inhibiting TAM, MET and AXL kinases improves antigen presentation and T lymphocytes *in vitro* effector functions. It is also known that blocking VEGF-dependent neoangiogenesis facilitates chemotaxis of lymphocytes and their infiltration of the tumour microenvironment [39]. In May 2020, during the ASCO virtual congress, Neeraj Agarwal et al. [40] presented the results of the multi-centre phase I/II COSMIC 021 study, which assessed the activity of atezolizumab (1200 mg IV q3w) combined with cabozantinib

(40 mg qd) in treatment of patients with advanced solid tumours. The primary endpoint of the study was ORR. The presented cohort included 44 mCRPC patients in good performance status (ECOG 0-1), with disease progression in soft tissues on enzalutamide or abiraterone. Patients did not previously receive cabozantinib, immunotherapy or chemotherapy (except for docetaxel used in the stage of castration sensitivity). Most of the patients had visceral or extra-regional lymph nodes metastases. Half of the patients previously received both abiraterone and enzalutamide, and 27% of the patients previously received docetaxel. The objective response rate in the study population was 32%, including 6.8% of complete responses. The disease control rate was 80%. The median duration of response was 8.6 months. The toxicity profile was predictable: 59% of patients experienced grade 3 and 4 toxicities, and 9% of immuno-related adverse events. The combination is currently being evaluated in a phase III study.

PARP inhibitors

Inactivating mutations in genes with known DNA repair function based on homologous recombinational repair mechanism (HRR) have long been studied in the context of their effect on carcinogenesis. These studies, however, were initially limited to cancers characteristic for multiple neoplasia syndromes associated with hereditary, germinal *BRCA1* and *BRCA2* genes mutations (mainly ovarian and breast cancers). Other neoplasms characterized by a high frequency of HRR genes alterations, both germinal and somatic, have been identified relatively recently. Up to 10% of prostate cancers are associated with an inherited *BRCA1* and *BRCA2* genes mutations, however, the latest studies indicate that the percentage of somatic mutations in all HRR genes in prostate cancer is much higher — they were identified in up to 25% of metastases. The *BRCA2* gene mutation is an independent, unfavourable prognostic factor in patients with prostate cancer, and the prognostic significance of other HRR defects is not fully known yet [41].

Simultaneous impairment of homologous recombination and DNA single-strand break repair (SSBR) processes by base excision repair (BER) leads to progressive degradation of DNA and cell death. Stimulation of BER mechanisms activity is one of the functions of enzymes from the group of poly-ADP-ribose polymerases (PARP). Physiologically, PARP binds to a single-stranded DNA damage site and mediates subsequent binding of the repair enzyme complex. Then, during the repair process itself, PARP must unbind from the DNA. PARP inhibitors (PARPi) not only impair the recruitment of a free repair complex but also stabilize the binding of PARP to DNA. Since the stable PARP-DNA complex is an obstacle to the DNA polymerase complex, PARP inhibitors not only prevent damage repair with the use of the BER mechanism but also prevent replication. In a cell with properly functioning other repair mechanisms, such a region will be completely excised, and the resulting double-strand break will be repaired by synthesizing the missing fragment similar to the same region of the sister chromatid (homologous recombination). In HRR defective cells, PARPi cause permanent, lethal damage to the genome.

At the ESMO 2018 Annual Meeting, Wassim Abida et al. [42, 43] presented the preliminary results of a single-armed phase 2 TRITON-2 study, evaluating the activity of PARPi, rucaparib in the treatment of patients with multi-line resistant metastatic prostate cancer and inactivating *BRCA1*, *BRCA2* or *ATM* genes mutations. The study recruited patients with mCRPC who previously received 1 line of docetaxel-based chemotherapy and 1–2 lines of next-generation anti-androgen therapy. The co-primary endpoints were ORR rate, both radiological and PSA.

Out of 25 patients with *BRCA* mutations, as many as 11 (44%) achieved a partial response, and another 9 (36%) achieved disease stabilization. In 5 patients with the *ATM* mutation, no objective responses were observed, but 4 patients (80%) achieved disease stabilization. The safety profile was predictable and 15.3% of patients experienced severe anaemia. The incidence of other serious adverse reactions was < 5%. Based on the results of the TRITON-2 study FDA granted accelerated approval to rucaparib.

In April 2020, Johann de Bono et al. [44] published in the "NEJM" the results of the phase III PROFOUND study. The study recruited mCRPC patients after failure of either abiraterone or enzalutamide-based hormone therapy. Previous chemotherapy with docetaxel was also allowed. The inclusion criterion was the presence in the tumour cells of at least one mutation of the HRR genes: *BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*. HRR genes alterations were identified in 778 patients (28% examined), 387 of whom met the inclusion criteria. Patients were included in two cohorts: A — 245 patients with *BRCA1*, *BRCA2*, *ATM* mutations; B — 142 patients with alteration in other genes. Patients in both cohorts were randomized in a 2:1 ratio to olaparib (300 mg bid) or treatment with a new anti-androgen: abiraterone (1000 mg/d) or enzalutamide (160 mg/d). The primary endpoint was rPFS in cohort A. Secondary endpoints were: OS, radiological, biochemical and cytometric response rates (defined as a decrease in circulating tumour cells from ≥ 5/7.5 mL to < 5/7.5 mL).

The study met its primary endpoint. In cohort A, median rPFS was significantly different in favour of olaparib: 7.4 months *vs.* 3.6 months (HR = 0.34; 95% CI, 0.25–0.47; p < 0.001), in the entire study pop-

ulation the difference in median rPFS was smaller, but still significant: 5.8 months *vs.* 3.5 months, respectively (HR = 0.49; 95% CI; 0.38–0.63; p < 0.001). The use of olaparib was associated with a significant increase in ORR in cohort A: 33% *vs.* 2% (OR 20.86; 95% CI, 4.18–379.18; p < 0.001), and in the entire population: 22% *vs.* 4% (OR 5.93; 95% CI; 2.01–25.4). In interim analysis (for data maturity approximately 40%), median OS in cohort A was 18.5 months *vs.* 15.1 months (HR = 0.64; 95% CI, 0.43–0.97; p = 0.02), and in the entire population 17.5 months *vs.* 14.3 months (HR = 0.67; 95% CI; 0.49–0.93). Significant differences in OS were observed even though approximately 80% of patients in the control arm received olaparib after progression. Adverse events were more frequent in the PARP inhibitor arm: grade 1–4 AEs were reported in 95% and 88% of patients, and grade ≥ 3, in 51% *vs.* 38% patients in the PARPi and placebo arm, respectively. The most common AEs in the active treatment arm included anaemia, nausea, and fatigue/asthenia, whilst in the control arm there was fatigue/asthenia. One side effect-related death was noted in each study arm. Based on the results of the PROFOUND study, olaparib was approved by the FDA and EMA for the treatment of mCRPC patients after the failure of modern hormone therapy. In the US, the drug is used in patients with germinal or somatic mutations in the HRR genes, and in Europe only in patients with germinal or somatic *BRCA1* or *BRCA2* genes mutations.

The remaining PARPi: niraparib and talazoparib, showed promising activity in the dHRR population in phase II studies and are currently being evaluated in randomized trials [45].

Summary

Systemic treatment is evolving towards strategies that are increasingly selective for tumour tissue and at the same time more personalized. A better understanding of the mechanisms responsible for prostate cancer carcinogenesis has resulted in an unprecedented rate of new therapeutic options emergence in the last two decades. The reliability of AR-dependent signalling pathways blocking, offered by new molecules, has resulted in an extension of the period measured in years in which patients can be offered active therapies, not adversely affecting the quality of life. Advances in nuclear medicine resulted in the development of sensitive radiotracers as well as therapeutic isotopes which prolong overall survival. Research on the role of HRR allowed patients with other types of cancer to take advantage of the PARPi activity.

However, there are still many challenges. The use of new generation antiandrogens is associated with a more frequent occurrence of cancers completely independent of androgen signalling, showing small-cell or neuroendocrine features. The incidence of prostate cancer is also increasing in relatively young patients who need much more aggressive and long-acting therapeutic strategies. The new therapies generate a considerable strain on the healthcare system finances. Finally, treatment personalization itself contributes to the atomization of therapeutic algorithms, makes it difficult to qualify patients for clinical trials, forcing an even narrower sub-specialization and greater expenditure of time spent on lifelong learning. At the beginning of the third decade of the 21st century, we will have to overcome these problems.

Conflict of interest

Paweł Potocki received honoraria and travel grants from Astellas, Astra Zeneca, Bayer, Janssen, MSD, Merck, Roche.

Piotr Wysocki received honoraria, travel grants and research funding from Astellas, Astra Zeneca, Janssen, Ipsen, Roche, Sanofi, Bayer.

References

1. Adams J. The case of scirrhous of the prostate gland with corresponding affliction of the lymphatic glands in the lumbar region and in the pelvis. Lancet. 1853; 1(1): 393.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
3. White JW. II. The Present Position of the Surgery of the Hypertrophied Prostate. Ann Surg. 1893; 18(2): 152–188, doi: 10.1097/00000658-189307000-00020, indexed in Pubmed: 17859954.
4. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972; 22(4): 232–240, doi: 10.3322/canjclin.22.4.232, indexed in Pubmed: 4625049.
5. Mainwaring WI. A soluble androgen receptor in the cytoplasm of the male mastomys prostate. Urol Res. 1978; 6(1): 29–33, doi: 10.1007/BF00257079, indexed in Pubmed: 644728.
6. Schally AV, Kastin AJ, Arimura A. Hypothalamic follicle-stimulating hormone (FSH) and luteinizing hormone (LH)-regulating hormone: structure, physiology, and clinical studies. Fertil Steril. 1971; 22(11): 703–721.
7. Messner EA, Steele TM, Tsamouri MM, et al. The androgen receptor in prostate cancer: Effect of structure, ligands and spliced variants on therapy. Biomedicines. 2020; 8(10), doi: 10.3390/biomedicines8100422, indexed in Pubmed: 33076388.
8. Thadani-Mulero M, Nanus DM, Giannakakou P. Androgen receptor on the move: boarding the microtubule expressway to the nucleus. Cancer Res. 2012; 72(18): 4611–4615, doi: 10.1158/0008-5472.CAN-12-0783, indexed in Pubmed: 22987486.
9. Seruga B, Ocana A, Tannock IF. Drug resistance in metastatic castration-resistant prostate cancer. Nat Rev Clin Oncol. 2011; 8(1): 12–23, doi: 10.1038/nrclinonc.2010.136, indexed in Pubmed: 20859283.
10. Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): a semisynthetic analogue of taxol. J Natl Cancer Inst. 1991; 83(4): 288–291, doi: 10.1093/jnci/83.4.288, indexed in Pubmed: 1671606.
11. Bai S, Zhang BY, Dong Y. Impact of taxanes on androgen receptor signaling. Asian J Androl. 2019; 21(3): 249–252, doi: 10.4103/aja.aja_37_18, indexed in Pubmed: 29900882.

12. Tannock I, Wit Rde, Berry W, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. New England Journal of Medicine. 2004; 351(15): 1502–1512, doi: 10.1056/nejmoa040720.
13. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008; 26(2): 242–245, doi: 10.1200/JCO.2007.12.4008, indexed in Pubmed: 18182665.
14. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors. Clin Cancer Res. 2009; 15(2): 723–730, doi: 10.1158/1078-0432.CCR-08-0596, indexed in Pubmed: 19147780.
15. Bono Jde, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010; 376(9747): 1147–1154, doi: 10.1016/s0140-6736(10)61389-x.
16. de Wit R, de Bono J, Sternberg CN, et al. CARD Investigators. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019; 381(26): 2506–2518, doi: 10.1056/NEJMoa1911206, indexed in Pubmed: 31566937.
17. Cabazitaxel versus the switch to alternative ar-targeted agent (enzalutamide or abiraterone) in metastatic castration-resistant prostatę cancer (mCRPC) patients previously treated with docetaxel and who rapidly failed a prior ar-targeted agent (CARD), https://clinicaltrials.gov/ct2/show/NCT02485691 (26.01.2021).
18. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368: 138–148, doi: 10.1056/NEJMoa1209096.
19. Ryan CJ, Smith MR, Fizazi K, et al., "Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015; 16 (2): 152–160P. doi: 10.1016/S1470-2045(14)71205-7.
20. Fizazi K, Scher H, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology. 2012; 13(10): 983–992, doi: 10.1016/s1470-2045(12)70379-0.
21. Ryan C, Smith MR, Fizazi K, et al. Final Overall survival analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy. ESMO 2014; Abstract 7530 (oral presentation).
22. Attard G, Borre M, Gurney H, et al. PLATO collaborators. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol. 2018; 36(25): 2639–2646, doi: 10.1200/JCO.2018.77.9827, indexed in Pubmed: 30028657.
23. Morris M, Heller G, Bryce A, et al. Alliance A031201: A phase III trial of enzalutamide (ENZ) versus enzalutamide, abiraterone, and prednisone (ENZ/AAP) for metastatic castration resistant prostate cancer (mCRPC). Journal of Clinical Oncology. 2019; 37(15_suppl): 5008–5008, doi: 10.1200/jco.2019.37.15_suppl.5008.
24. Scher HI, Fizazi K, Saad F, et al. AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012; 367(13): 1187–1197, doi: 10.1056/NEJMoa1207506, indexed in Pubmed: 22894553.
25. Beer TM, Armstrong AJ, Rathkopf DE, et al. PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014; 371(5): 424–433, doi: 10.1056/NEJMoa1405095, indexed in Pubmed: 24881730.
26. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL Study. Eur Urol. 2017; 71(2): 151–154, doi: 10.1016/j.eururo.2016.07.032, indexed in Pubmed: 27477525.
27. Smith MR, Antonarakis ES, Ryan CJ, et al. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. Eur Urol. 2016; 70(6): 963–970, doi: 10.1016/j.eururo.2016.04.023, indexed in Pubmed: 27160947.
28. Fizazi K, Massard C, Bono P, et al. Safety and Antitumour Activity of ODM-201 (BAY-1841788) in Castration-resistant, CYP17 Inhibitor-naïve Prostate Cancer: Results from Extended Follow-up of the ARADES Trial. Eur Urol Focus. 2017; 3(6): 606–614, doi: 10.1016/j.euf.2017.01.010, indexed in Pubmed: 28753849.
29. Sgouros G, Hobbs R, Josefsson A. Dosimetry and Radiobiology of Alpha-Particle Emitting Radionuclides. Curr Radiopharm. 2018; 11(3): 209–214, doi: 10.2174/1874471011666180426130058, indexed in Pubmed: 29697036.
30. Godlewski T. A new radio-active product from actinium. Nature. 1905; 71(1839): 294–295, doi: 10.1038/071294b0.
31. Morris MJ, Corey E, Guise TA, et al. Radium-223 mechanism of action: implications for use in treatment combinations. Nat Rev Urol. 2019; 16(12): 745–756, doi: 10.1038/s41585-019-0251-x, indexed in Pubmed: 31712765.
32. Parker C, Nilsson S, Heinrich D, et al. ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013; 369(3): 213–223, doi: 10.1056/NEJMoa1213755, indexed in Pubmed: 23863050.
33. Parker CC, Coleman RE, Sartor O, et al. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial. Eur Urol. 2018; 73(3): 427–435, doi: 10.1016/j.eururo.2017.06.021, indexed in Pubmed: 28705540.
34. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol. 2006; 24(19): 3089–3094, doi: 10.1200/JCO.2005.04.5252, indexed in Pubmed: 16809734.
35. Kantoff PW, Higano CS, Shore ND, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363(5): 411–422, doi: 10.1056/NEJMoa1001294, indexed in Pubmed: 20818862.
36. Beer TM, Kwon ED, Drake CG, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol. 2017; 35(1): 40–47, doi: 10.1200/JCO.2016.69.1584, indexed in Pubmed: 28034081.
37. Kwon ED, Drake CG, Scher HI. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014; 15(7): 700–712, doi: 10.1016/S1470-2045(14)70189-5.
38. Antonarakis E, Piulats J, Gross-Goupil M, et al. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. J Clin Oncol. 2020; 38(5): 395–405, doi: 10.1200/jco.19.01638.
39. Bergerot P, Lamb P, Wang E, et al. Cabozantinib in Combination with Immunotherapy for Advanced Renal Cell Carcinoma and Urothelial Carcinoma: Rationale and Clinical Evidence. Mol Cancer Ther. 2019; 18(12): 2185–2193, doi: 10.1158/1535-7163.MCT-18-1399, indexed in Pubmed: 31792125.
40. Agarwal N, Loriot Y, McGregor B, et al. Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results of cohort 6 of the COSMIC-021 study. J Clin Oncol. 2020; 38(15_suppl): 5564–5564, doi: 10.1200/jco.2020.38.15_suppl.5564.
41. Armenia J, Wankowicz SAM, Liu D, et al. PCF/SU2C International Prostate Cancer Dream Team. The long tail of oncogenic drivers in prostate cancer. Nat Genet. 2018; 50(5): 645–651, doi: 10.1038/s41588-018-0078-z, indexed in Pubmed: 29610475.
42. Abida W, Bryce AH, Vogelzang NJ, et al. 793PDPreliminary results from TRITON2: A phase II study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations. Ann. Oncol., 2018; 29 (suppl_8): 2018P. doi: 10.1093/annonc/mdy284.002.
43. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration abstract. 2020; 2P doi: 10.1200/JCO.20.01035.
44. Bono Jde, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM. 2020; 382(22): 2091–2102, doi: 10.1056/nejmoa1911440.
45. Smith M, Sandhu S, Kelly W, et al. Phase II study of niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD): Preliminary results of GALAHAD. J Clin Oncol. 2019; 37(7_suppl): 202–202, doi: 10.1200/jco.2019.37.7_suppl.202.

VIA MEDICA

REVIEW ARTICLE

Roman Dubiański

Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw

Effect of ribociclib plus fulvestrant on overall survival in the treatment of advanced breast cancer — updated MONALEESA-3 results

Address for correspondence:
Roman Dubiański, MD PhD
Department of Breast Cancer
and Reconstructive Surgery,
Maria Sklodowska-Curie National Research
Institute of Oncology, Warsaw
W. K. Roentgena 5 St., 02–781 Warsaw,
Poland
e-mail: r.dubianski@hotmail.com

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice
DOI: 10.5603/OCP.2021.0034

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

The results of the treatment of ER-positive/HER2-negative advanced breast cancer have been improved in the last few years due to the use of CDK4/6 inhibitors combined with endocrine therapy. Ribociclib with fulvestrant significantly prolonged progression-free survival and overall survival in the phase-III MONALEESA-3 trial. The newest update of the trial (after 56.3 months of observation) showed significant improvement in overall survival in the experimental arm for more than a year: mOS was 53.7 months in the ribociclib plus fulvestrant arm and 41.5 months in the placebo plus fulvestrant arm (risk reduction of 27%). Subgroup analysis confirmed the efficacy of the treatment in both the first and second lines of treatment. The study also showed that adding ribociclib to the endocrine treatment prolongs the median time to chemotherapy. No new toxicities were observed in longer observation.

Key words: breast cancer, ribociclib, fulvestrant, CDK4/6 inhibitor

Oncol Clin Pract 2022; 18, 3: 189–194

Introduction

There are many molecular pathways in breast cancer cells that could be blocked by targeted drugs, for example, cyclin-dependent kinases 4/6 (CDK 4/6) inhibitors. The complex interactions between cyclins and CDKs control the cell life cycle because these enzymes play a regulatory role at all stages of cell division. The initiation of division depends primarily on kinases 4 and 6 (CDK 4 and 6), which are structurally related and have similar biological and biochemical properties [1]. Changes in the cell cycle are typical of malignant neoplasms, including its disruption leading to uncontrolled growth. Numerous changes in regulatory proteins and disturbances in the regulation of the cyclin D1:CDK4/6 axis have been described in breast cancer cells [2–4]. Activation of this axis is characteristic of luminal breast cancer, in which cells contain more cyclin D than in other types of breast cancer [5]. There is evidence concerning conduction between ER and cyclin D1 (CCND1) pathways in ER-positive breast cancer cells [6]. Inhibition of CDKs has become an important target of new treatments for breast cancer patients. Initially, non-specific CDK inhibitors were used; however, their value assessed in clinical trials was unsatisfactory [7, 8]. Only the use of specific second-generation inhibitors targeting CDK4/6 showed very promising results. CDK4/6 inhibitors currently available for the

Received: 16.11.2021 Accepted: 16.11.2021 Early publication date: 27.05.2022

treatment of patients with ER+/HER2- breast cancer include abemaciclib, palbociclib, and ribociclib.

Ribociclib is a highly selective CDK4/6 inhibitor, which in preclinical studies showed high activity in solid tumors (including ER+/HER2- advanced breast cancer) [9]. *In vitro* and *in vivo* studies in humans have shown that it is metabolized in the liver (mainly via CYP3A4). Ribociclib and its metabolites are mainly excreted in the feces and, to a small extent, via the kidneys.

Three phase-III studies were conducted, which aimed at confirming the effectiveness of ribociclib in the treatment of patients with advanced breast cancer. The first was the phase-III MONALEESA-2 study, which involved patients with hormone-dependent and HER2-negative advanced breast cancer, who did not previously receive systemic treatment due to the disease progression [10]. The study enrolled 668 patients randomly assigned to treatment with ribociclib in combination with letrozole or with letrozole as monotherapy. The primary endpoint was progression-free survival, which was significantly longer in the ribociclib arm; the 18-month PFS rate was 63% [95% CI (confidence interval) 54.6–70.3] versus 42.2% with a 95% CI of 34.8–49.5 in the placebo group, and the median PFS was 14.7 months (95% CI 13.0–16.5) in the placebo group (in experimental group median OS was not reached). In the updated analysis, after a median follow-up of 26.4 months, the median PFS was 25.3 months in the experimental arm and 16 months in the control arm, which corresponded to a hazard ratio (HR) of 0.568; 95% CI 0.457–0.704; $p = 9.63 \times 10^{-8}$ [11]. The study showed an improvement in overall survival (OS) which was a secondary endpoint. During the ESMO (European Society for Medical Oncology) Congress 2021, the updated results of the study were presented, which showed an extension of OS in the group receiving combination treatment; the median was 63.9 months *vs.* 51.4 months (HR 0.76; 95% CI 0.63–0.93; p = 0.004) [12]. It was an outstanding observation, showing that patients with advanced breast cancer could survive for more than 5 years.

On the other hand, the MONALEESA-7 study was the first phase-III study with a CDK4/6 inhibitor, recruiting only premenopausal or perimenopausal patients [13]. The study included 672 patients who could receive hormone therapy or chemotherapy as neo- or adjuvant treatment, and one line of chemotherapy for advanced disease. Patients received either ribociclib in combination with tamoxifen or an aromatase inhibitor (letrozole or anastrozole) and goserelin, or hormone therapy alone in the control arm. The primary endpoint was PFS, whose median in the ribociclib arm was 23.8 months vs. 13 months for placebo (HR 0.55; 95% CI 0.44–0.69; p < 0.0001). The first data on the addition of ribociclib to hormone therapy in the MONALEESA-7 study showed a significant increase in OS compared to hormone therapy and placebo. The OS rate at 42 months of follow-up was 70.2% in the ribociclib group (95% CI 63.5–76.0) and 46% (95% CI 32.0–58.9) for placebo (HR 0.71; 95% CI 0.54–0.95; p = 0.00973) [14]. The median OS was not reached in the ribociclib arm at this time point. Further updated results of the MONALEESA-7 study were presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2020 [15]. After an additional mean follow-up of 53.5 months, the median OS in the experimental arm was 58.7 months and was more than 10 months longer than in the placebo arm (48 months; HR, 0.76; 95% CI 0.61–0.96).

The MONALEESA-3 study was the third trial in which ribociclib was used in the treatment of advanced ER+/HER2– breast cancer. This article aims to present an overview of this study and its updated results.

MONALEESA-3 study

MONALEESA-3 is a phase-III clinical study investigating the efficacy of ribociclib in combination with fulvestrant and including 726 postmenopausal patients. The included patients had histopathologically-confirmed, generalized, or locally advanced ER+/HER2- breast cancer, ineligible for local treatment. The study included patients with newly diagnosed advanced ER+/HER2- breast cancer, with relapse during or at least 12 months after the completion of neoadjuvant or adjuvant hormone therapy, and patients previously treated with one line of hormone therapy for advanced breast cancer[16]. A summary of indications for prior treatment is presented in Table 1.

Other inclusion criteria included the presence of measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) or at least one lytic bone lesion, performance status according to Eastern Cooperative Oncology Group scoring sys-

Table 1. Distribution of patients participating in MONALEESA-3 according to prior treatment for breast cancer

First-line treatment	*De novo* diagnosed advanced breast cancer
	Relapse more than 12 months after completion of neoadjuvant or adjuvant hormone therapy
Second-line treatment	Relapse during neoadjuvant or adjuvant hormone therapy or less than 12 months after completion
	Progression after a single line of hormone therapy for advanced breast cancer without prior neoadjuvant or adjuvant hormone therapy
	Progression after a single line of hormone therapy for advanced breast cancer in patients with relapse more than 12 months after completion of neoadjuvant or adjuvant hormone therapy

tem (ECOG PS) 0 or 1. Patients previously receiving chemotherapy for advanced breast cancer, before the fulvestrant or CDK4/6 inhibitor, as well as with clinically significant arrhythmias and uncontrolled cardiovascular diseases, were excluded from the study.

Patients were randomly assigned (2:1) either to the experimental arm with ribociclib and fulvestrant (484 patients) or the control arm with fulvestrant and placebo (242 patients). Patients received 500 mg of fulvestrant intramuscularly (day 1 of the 28-day cycle and additionally on day 15 of cycle 1) and either placebo or ribociclib at a dose of 600 mg/day according to a 3-weeks-on/1-week-off schedule. The primary endpoint of the study was PFS. The median PFS was significantly greater in the ribociclib group compared to the placebo group: 20.5 months *vs.* 12.8 months (HR 0.593; 95% CI 0.480-0.732; P=0.00000041) [16]. The obtained results led to very fast approval of ribociclib in combination with fulvestrant as the first- and second-line treatment of patients with advanced breast cancer. The secondary much-awaited endpoint of the study was OS because it is not always possible to achieve OS prolongation in oncology even with a significant extension of PFS. Additionally, the MONALEESA-3 study also assessed: PFS2 (time from the randomization to the first documented disease progression during the next line of treatment or death from any cause), time to chemotherapy use (measured from the randomization to receiving the first chemotherapy after completing the study treatment), and chemotherapy-free survival (time to the first chemotherapy or death). The assumptions of the study also included OS subgroups analysis (patients receiving first-line and second-line treatment, patients with hormone sensitivity and hormone resistance, and patients with or without lung and/or liver metastases). Median OS and OS duration were estimated using the Kaplan-Meier method.

The first results of the MONALEESA-3 study for OS were presented at the ESMO Congress 2019 and published in full in the New England Journal of Medicine [17]. OS was significantly improved in patients receiving ribociclib in combination with fulvestrant. After 42 months of follow-up, an improvement in OS rate was evident in patients receiving combination therapy, 57,8% in the experimental arm compared to 45.9% in the control arm (HR 0.72; 95% CI 0.57–0.92; p = 0.00455). At the time of the first survival analysis, the median OS in the ribociclib arm was not reached, while it was 40 months in the placebo arm. The benefit of using ribociclib in combination with fulvestrant was demonstrated in both the first- (median OS for the ribociclib arm not reached, 45.1 months in the placebo arm; HR 0.70; 95% CI 0.479–1.021) and the second-line treatment (40.2 months for ribociclib with fulvestrant *vs.* 32.5 months for fulvestrant alone; HR 0.730; 95% CI 0.530–1.004).

The latest update of OS data was made after a median follow-up of 56.3 months (data cut-off: 30 October 2020) [18]. More than a year after the previous analysis, study treatment was still received by 14% of patients in the ribociclib arm and 8.7% of patients in the placebo arm, and death occurred in 45.9% and 58.7% of patients, respectively. There was a significant increase in median OS from 41.5 months in patients receiving placebo plus fulvestrant to 53.7 months in the group with ribociclib and fulvestrant (HR 0.73; 95% CI 0.59–0.90) (Fig. 1). Kaplan-Meier estimates of the 5-year survival rate were

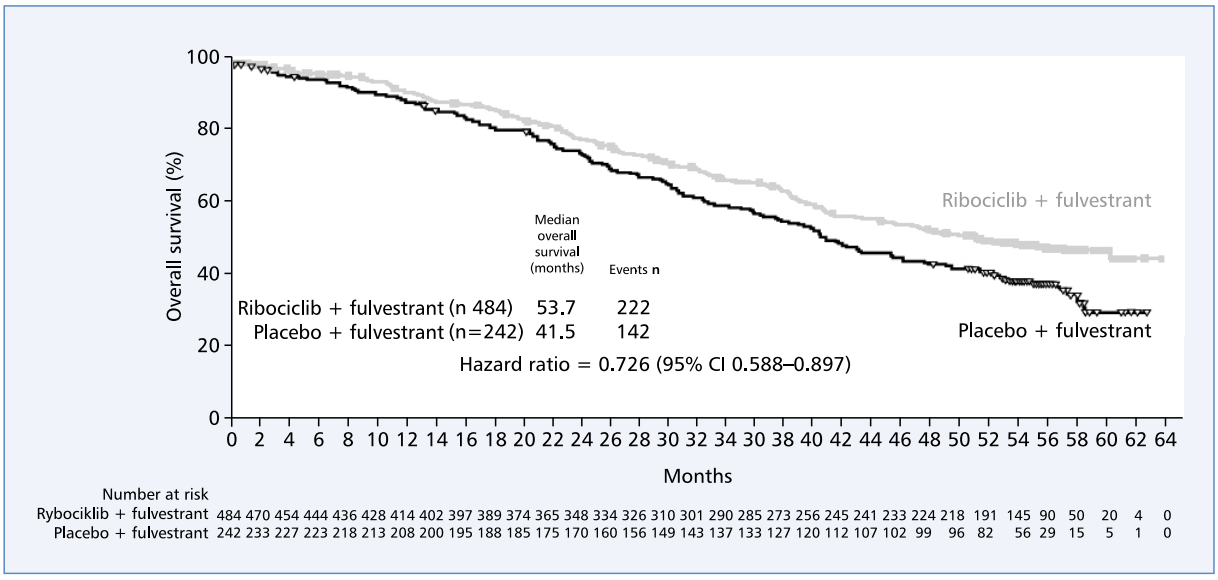

Figure 1. Overall survival in general population; CI — confidence interval

Table 2. Overall survival in individual groups of patients in the MONALEESA-3 study

	Median overall survival	
	ribociclib + fulvestrant (months)	**placebo + fulvestrant (months)**
First-line treatment	Not reached	51.8
Second-line treatment	39.7	33.7
Patients with lung/liver metastases	46.9	39.4
Patients with hormone resistance	35.6	31.7
Patients with hormone sensitivity	49	41.8
Hormone-naïve patients	59.9	50.9

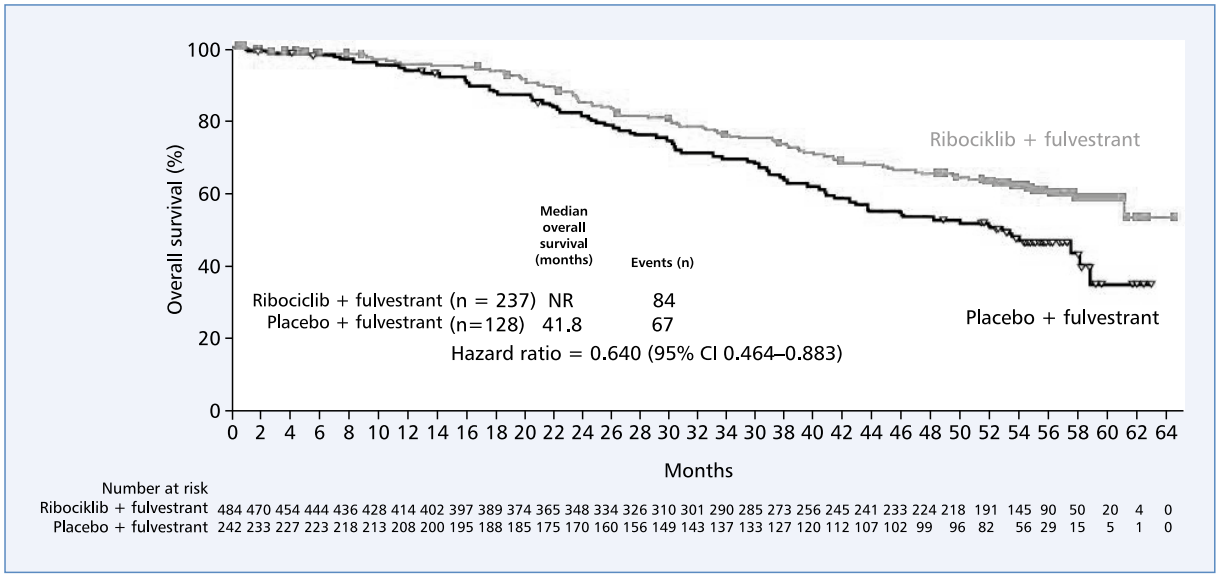

Figure 2. Overall survival in patients receiving ribociclib in combination with fulvestrant in first-line treatment; CI — confidence interval; NR — not reached

46% (95% CI 49–58%) in the experimental arm versus 31% (95% CI 23–40%) in the control arm.

Overall survival outcomes in individual patient subgroups from the most recent analysis are presented in Table 2 and Figures 2 and 3.

Combination therapy with ribociclib and fulvestrant turned out to be more effective than fulvestrant as monotherapy, regardless of treatment line, previous hormone therapy, no use of hormonal drugs, as well as hormone resistance or hormone sensitivity. Factors that did not affect the efficacy of ribociclib were, among others, patient age and the number of metastases (OS prolongation was stratified according to under and over 65 years of age and fewer and more than three metastases).

In both arms, as many as 80% of patients after treatment completion received one or more subsequent treatment lines, with the most commonly used hormone therapy alone (28% in the ribociclib arm and 21% in the placebo arm), and chemotherapy as the second most common option (23 and 20%, respectively), followed by hormone therapy in combination with a molecularly targeted drug. Patients from both groups received the CDK4/6 inhibitor after study completion, more than twice as often in the control arm (30% *vs.* 14% in the ribociclib arm). Importantly, the time to chemotherapy was significantly longer (by almost 20 months) in the ribociclib arm (48.1 months) than in the placebo arm (28.8 months; HR 0.70; 95% CI 0.57–0.88). Chemotherapy-free survival (time to first chemotherapy or death) was 32.3 months in the experimental arm *vs.* 22.4 months in the placebo arm (HR 0.70; 95% CI 0.57–0.88) (Fig. 4). Regarding PFS2, another endpoint of the MONALEESA-3 study, the use of fulvestrant with ribociclib was also superior, with significant prolongation in the experimental arm (37.4 months compared to 28.1 months in the placebo group, HR 0.7069; 95% CI 0.57–0.84), which is another argument supporting the use of combination therapy.

The latest update of the MONALEESA-3 study does not provide a detailed discussion of treatment toxicity,

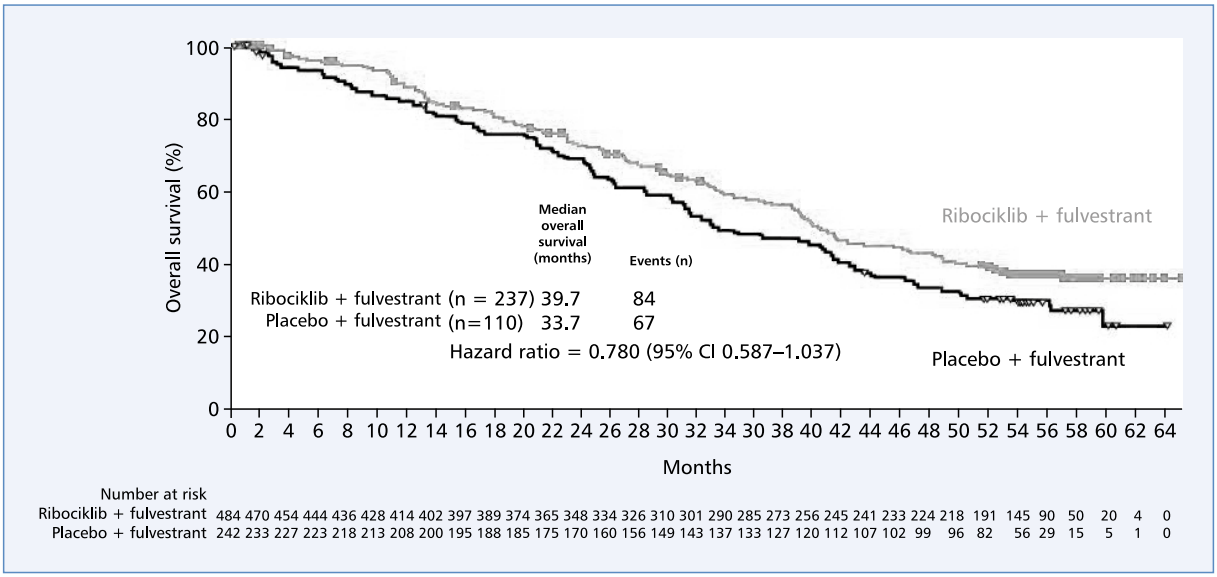

Figure 3. Overall survival in patients receiving ribociclib in combination with fulvestrant in second-line treatment; CI — confidence interval; NR — not reached

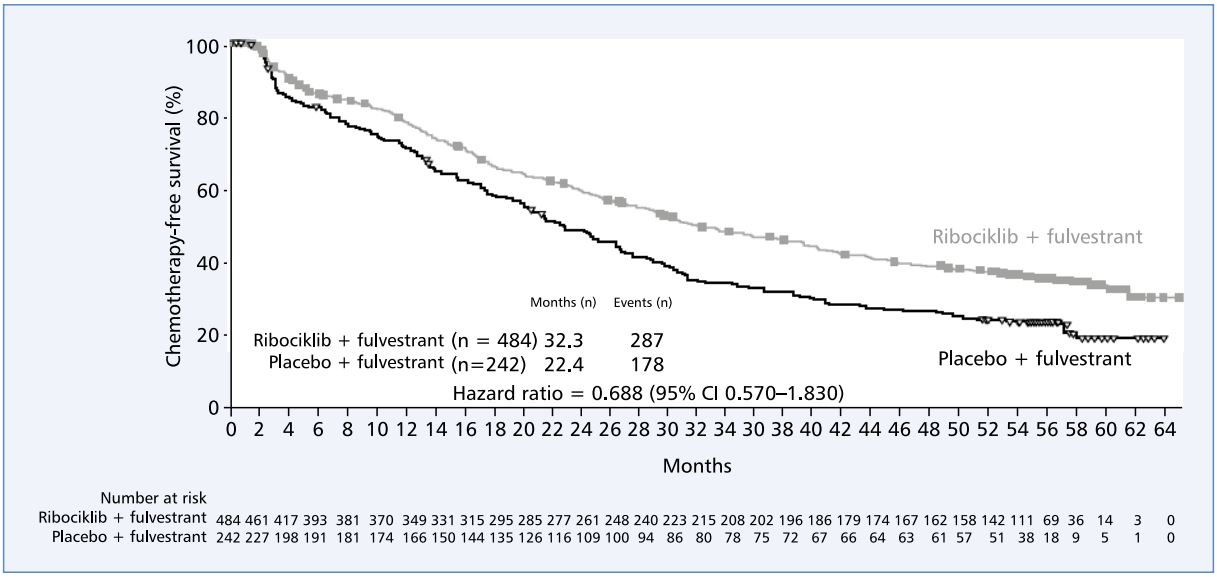

Figure 4. Chemotherapy-free survival; CI — confidence interval

as the extended follow-up did not reveal any additional or significant data in terms of side effects. The authors only confirm the toxicity profile of ribociclib, with neutropenia as the most common side effect, which occurred in grade 3 or 4 in 58.2% of patients (0.8% of patients in the placebo arm).

Discussion

The latest update of the MONALEESA-3 study, after an exceptionally long follow-up period (median 56.3 months) confirms the effectiveness of ribociclib with fulvestrant, already presented in the previous reports [16, 17], in patients with advanced ER-positive and HER2-negative breast cancer [18]. OS prolongation was achieved in patients receiving ribociclib in the first- and second-line treatment. The advantage of the combination treatment with ribociclib and fulvestrant was confirmed in all subgroups (including patients with metastases in parenchymal organs, for whom chemotherapy is still too often used in clinical practice). Other subgroups with prolonged OS included patients with hormone resistance and hormone sensitivity, as well as elderly patients, who unfortunately commonly receive less intensive treatment. It has also been shown that the

addition of ribociclib to hormone therapy with fulvestrant significantly prolongs the time to chemotherapy and in practice extends the time to treatment initiation, much more often associated with the occurrence of side effects and deterioration of the quality of life. In conclusion, the most recent data on treatment with ribociclib in combination with fulvestrant, indicating the prolongation of OS by more than one year, may support using this treatment regimen in clinical practice in patients with advanced ER-positive and HER2-negative breast cancer. According to the latest guidelines, a combination of CDK4/6 inhibitor with hormone therapy is the standard of care in the first-line treatment in patients with advanced breast cancer and should be used in all patients who do not require chemotherapy due to the presence of a visceral crisis [19–21].

Conflict of interest

Advisory boards, lectures, conferences: Novartis, Accord, Eli Lilly, Pfizer, Roche, Amgen, Egis, Pierre Fabre.

References

1. Pavletich NP. Mechanisms of cyclin-dependent kinase regulation: structures of Cdks, their cyclin activators, and Cip and INK4 inhibitors. J Mol Biol. 1999; 287(5): 821–828, doi: 10.1006/jmbi.1999.2640, indexed in Pubmed: 10222191.
2. Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. J Clin Oncol. 2005; 23(18): 4215–4224, doi: 10.1200/JCO.2005.05.064, indexed in Pubmed: 15961768.
3. Yu Q, Sicinska E, Geng Y, et al. Requirement for CDK4 kinase function in breast cancer. Cancer Cell. 2006; 9(1): 23–32, doi: 10.1016/j.ccr.2005.12.012, indexed in Pubmed: 16413469.
4. Landis MW, Pawlyk BS, Li T, et al. Cyclin D1-dependent kinase activity in murine development and mammary tumorigenesis. Cancer Cell. 2006; 9(1): 13–22, doi: 10.1016/j.ccr.2005.12.019, indexed in Pubmed: 16413468.
5. Agarwal R, Gonzalez-Angulo AM, Myhre S, et al. Integrative analysis of cyclin protein levels identifies cyclin b1 as a classifier and predictor of outcomes in breast cancer. Clin Cancer Res. 2009; 15(11): 3654–3662, doi: 10.1158/1078-0432.CCR-08-3293, indexed in Pubmed: 19470724.
6. Eeckhoute J, Carroll JS, Geistlinger TR, et al. A cell-type-specific transcriptional network required for estrogen regulation of cyclin D1 and cell cycle progression in breast cancer. Genes Dev. 2006; 20(18): 2513–2526, doi: 10.1101/gad.1446006, indexed in Pubmed: 16980581.
7. Tan AR, Yang X, Berman A, et al. Phase I trial of the cyclin-dependent kinase inhibitor flavopiridol in combination with docetaxel in patients with metastatic breast cancer. Clin Cancer Res. 2004; 10(15): 5038–5047, doi: 10.1158/1078-0432.CCR-04-0025, indexed in Pubmed: 15297405.
8. Mita MM, Joy AA, Mita A, et al. Randomized phase II trial of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus capecitabine in patients with advanced breast cancer. Clin Breast Cancer. 2014; 14(3): 169–176, doi: 10.1016/j.clbc.2013.10.016, indexed in Pubmed: 24393852.
9. Infante JR, Cassier PA, Gerecitano JF, et al. A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin Cancer Res. 2016; 22(23): 5696–5705, doi: 10.1158/1078-0432.CCR-16-1248, indexed in Pubmed: 27542767.
10. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016; 375(18): 1738–1748, doi: 10.1056/NEJMoa1609709, indexed in Pubmed: 27717303.
11. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018; 29(7): 1541–1547, doi: 10.1093/annonc/mdy155, indexed in Pubmed: 29718092.
12. Hortobagyi GN, Stemmer SM, Burris HA, et al. LBA17 Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology. 2021; 32: S1290–S1291, doi: 10.1016/j.annonc.2021.08.2090.
13. Tripathy D, Bardia A, Hurvitz SA, et al. Phase III, randomized, double-blind, placebo-controlled study of ribociclib (LEE011) in combination with either tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with HR+, HER2-advanced breast cancer (aBC): MONALEESA-7. J Clin Oncol. 2015; 33(supl 15).
14. Harbeck N, Franke F, Villanueva-Vazquez R, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018; 19(7): 904–915, doi: 10.1016/S1470-2045(18)30292-4, indexed in Pubmed: 29804902.
15. Tripathy D, Im SA, Colleoni M, et al. Abstract PD2-04: Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. Poster Spotlight Session Abstracts. 2021, doi: 10.1158/1538-7445.sabcs20-pd2-04.
16. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018; 36(24): 2465–2472, doi: 10.1200/JCO.2018.78.9909, indexed in Pubmed: 29860922.
17. Slamon D, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020; 382(6): 514–524, doi: 10.1056/nejmoa1911149.
18. Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. Ann Oncol. 2021; 32(8): 1015–1024, doi: 10.1016/j.annonc.2021.05.353, indexed in Pubmed: 34102253.
19. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020; 31(12): 1623–1649, doi: 10.1016/j.annonc.2020.09.010, indexed in Pubmed: 32979513.
20. Jassem J, Krzakowski M, Bobek-Bilewicz B, et al. Breast cancer. Oncol Clin Pract. 2020; 16(5), doi: 10.5603/OCP.2020.0038.
21. Gennari A, André F, Barrios CH, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021 [Epub ahead of print], doi: 10.1016/j.annonc.2021.09.019, indexed in Pubmed: 34678411.

Barbara Radecka

Department of Oncology, Institute of Medical Sciences, University of Opole, Opole, Poland
Tadeusz Koszarowski Cancer Center in Opole, Department of Oncology with Daily Unit, Opole, Poland

Commentary

to *Effect of ribociclib plus fulvestrant on overall survival in the treatment of advanced breast cancer — updated MONALEESA-3 results*

Inhibitors of cyclin-dependent kinases 4/6 (CDK 4/6) are currently widely used in the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2−) advanced breast cancer. The biological rationale for the benefit of this treatment has been supported by the results of several randomized controlled trials that have consistently shown an improvement in progression-free survival (PFS) for the three approved CDK 4/6 inhibitors (ribociclib, abemaciclib, and palbociclib). A benefit has been noticed in first-line and second-line treatment, in hormone-sensitive and hormone-refractory patients, in combination with an aromatase inhibitor (IA) or fulvestrant, and regardless of the patients' menopausal status. Obviously, the evaluation of the effect of these drugs on overall survival (OS) required a longer follow-up. The results of the MONALEESA-2 and MONALEESA-7 studies have recently been presented, which confirmed the improving OS by using ribociclib in combination with IA.

The design of these studies and the results to date supported using CDK 4/6 inhibitors in combination with IA in the first-line treatment and with fulvestrant in the second-line treatment. It should be noted, however, that the linearity of treatment was not always clearly defined in the studies; in MONARCH-2, the definition of treatment context was associated with sensitivity to hormone therapy, and the combination of fulvestrant with a CDK 4/6 inhibitor (abemaciclib in this case) was also administered in patients with relapse during (neo) adjuvant treatment or within 12 months of completing adjuvant treatment.

The MONALEESA-3 study is the first to investigate the combination of the CDK4/6 inhibitor ribociclib in combination with fulvestrant in first-line treatment [newly diagnosed advanced breast cancer or relapse more than 12 months after completion of (neo)adjuvant hormone therapy], and in this context, the treatment was used in almost half of the study population. It is important that the results of the phase-III FALCON study, which compared anastrozole with fulvestrant in first-line treatment, showed benefits of fulvestrant in terms of PFS (median PFS — 16.6 *vs.* 13.8 months, risk reduction by 20%, p = 0.049). This was especially true for patients without parenchymal metastases (median PFS — 22.3 *vs.* 13.8 months, risk reduction by 41%) [1].

The optimal timing for fulvestrant use in the therapeutic algorithm of patients with advanced HR+/HER2– breast cancer has not yet been clearly defined. Monotherapy with fulvestrant indicates its advantage over IA in patients who have not previously received hormone therapy due to advanced disease, while the combination of fulvestrant with a CDK4/6 inhibitor has so far been the preferred treatment option in patients after prior IA treatment. This approach is changed by the results of the MONALEESA-3 study, which was described in detail by Dubiański [2]. After a median follow-up of 56.3 months, the previously observed benefit of fulvestrant with ribociclib was confirmed with a statistically significant extension of the median OS

Received: 16.11.2021 Accepted: 16.11.2021 Early publication date: 27.05.2022

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice, DOI: 10.5603/OCP.2021.0035, Copyright © 2022 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

from 41.5 months in the placebo/fulvestrant group to 53.7 months in the ribociclib group in the general patient population (risk reduction by 27%) [3].

Subgroup analysis showed that the benefit of fulvestrant in combination with ribociclib was the highest in first-line patients. In this subgroup, median OS in the experimental arm was still not reached and median OS in the control arm was 51.8 months. In the subgroup of patients treated in the second line, the benefit of fulvestrant in combination with ribociclib is also numerically significant, but statistically insignificant (median — 39.7 *vs.* 33.7, respectively; risk reduction by 22% with a 95% confidence interval of 0.59–1.04).

The combination of fulvestrant with ribociclib is, therefore, becoming a valuable treatment option for patients not receiving prior hormone therapy due to advanced disease. It is also well-tolerated, safe, and maintains a good quality of life. However, it is not clear whether the use of fulvestrant as a hormonal partner for the CDK 4/6 inhibitor is the best option for all patients.

It is worth emphasizing that in recent years, oral preparations have been developed that belong to the group of selective estrogen receptor degraders (SERDs), which includes also fulvestrant. Study results indicate that they are more active than fulvestrant and show activity in patients with hormone resistance and the ESR1 mutation [4]. They are currently being intensively evaluated in clinical trials in combination with CDK4/6 inhibitors and phosphoinositide 3-kinase (PI3K) inhibitors. The next steps will be to identify non-estrogen receptor biomarkers that determine treatment response.

The introduction of CDK 4/6 inhibitors permanently changed the paradigm of treatment of patients with advanced HR+/HER2- breast cancer. These drugs are well-tolerated, and most side effects are generally manageable and resolve after dose reduction.

Real-word evidence observational studies can also provide valuable data, which will increase the knowledge regarding the implementation of these drugs in everyday practice.

References

1. Robertson J, Bondarenko I, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. The Lancet. 2016; 388(10063): 2997–3005, doi: 10.1016/s0140-6736(16)32389-3.
2. Dubiański R. Effect of ribociclib plus fulvestrant on overall survival in the treatment of advanced breast cancer- updated MONALEESA-3 results. Oncol Clin Pract, doi: 10.5603/OCP2021.0034.
3. Slamon DJ, Neven P, Chia S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. Ann Oncol. 2021; 32(8): 1015–1024, doi: 10.1016/j.annonc.2021.05.353, indexed in Pubmed: 34102253.
4. McDonnell DP, Wardell SE, Norris JD. Oral Selective Estrogen Receptor Downregulators (SERDs), a Breakthrough Endocrine Therapy for Breast Cancer. J Med Chem. 2015; 58(12): 4883–4887, doi: 10.1021/acs.jmedchem.5b00760, indexed in Pubmed: 26039356.

VIA MEDICA

REVIEW ARTICLE

Alice Indini[1], Fausto Roila[2], Rossana Gueli[1], Francesco Grossi[1, 3], Mario Mandalà[2]

[1]Division of Medical Oncology, Department of Medicine and Surgery, Ospedale di Circolo e Fondazione Macchi, ASST dei Sette Laghi, Varese, Italy
[2]Unit of Medical Oncology, Department of Surgery and Medicine, University of Perugia, Perugia, Italy
[3]Faculty of Medicine and Surgery, University of Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Italy

Targeted therapy for advanced cutaneous melanoma

Address for correspondence:
Prof. Mario Mandalà, M.D.
Unit of Medical Oncology University of Perugia, Perugia, Italy
e-mail: mario.mandala@unipg.it

Oncology in Clinical Practice
DOI: 10.5603/OCP.2022.0005

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Drugs targeting the mitogen-activated protein kinase (MAPK) pathway with BRAF and MEK inhibitors have significantly improved survival outcomes of patients with melanoma harboring *BRAF* V600 mutations. To date, three combination targeted therapies have been approved, based on the results of four randomized phase-III trials (COMBI-D, COMBI-V, CoBRIM, and COLUMBUS). In these trials, combined BRAF and MEK inhibitors demonstrated superiority as compared with BRAF inhibitor monotherapy and showed quite homogeneous data in terms of response rate (63%-70%), OS (median > 24 months), and PFS (median values ranging from 11 to 14 months). Consequently, different toxicity profiles of each combination therapy presently help with the decision-making process. Despite these successful results, treatment resistance represents an issue during both immunotherapy and targeted therapy, and there is presently no consensus on the therapeutic journey of patients with *BRAF* mutant melanoma to optimize their survival results. Several strategies to further increase therapeutic results of targeted therapy have been investigated, by combining and/or sequencing different treatment approaches. In this review, we will present the molecular features of cutaneous melanoma, focusing on *BRAF* mutation, the therapeutic rationale of targeted therapies, their efficacy, and toxicity, and give an overview of future perspectives in the treatment of this disease.

Key words: BRAF, MAPK, melanoma, metastatic disease, targeted therapies

Oncol Clin Pract 2022; 18, 3: 197–207

Introduction

Before the advances in the treatment of advanced/metastatic melanoma [i.e., unresectable stage III/stage IV disease according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition], disease outcomes with chemotherapy were very poor [1]. Historically, patients with advanced disease had median overall survival (OS) of approximately 7.5 months and a 5-year survival rate of ~6% [1]. Over the last decades, two therapeutic strategies have significantly improved survival outcomes of patients with metastatic melanoma. The first one involves modulating the immune system with monoclonal antibodies acting as immune-checkpoint inhibitors (ICIs), targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), or the programmed cell-death 1 (PD-1) [2–4]. The second class of drugs targets the mitogen-activated protein kinase (MAPK) pathway, which is constitutively active in melanomas harboring *BRAF* V600 mutations [5]. To date, targeted therapy with BRAF and MEK inhibitors represents the first choice of treatment for most patients with *BRAF* mutant melanoma due to the impressive survival results obtained in certain settings (e.g., patients with a low tumor burden). Several strategies to further increase therapeutic results of targeted therapy have been investigated by combining and/or sequencing different treatment approaches. Still, treatment resistance

Received: 26.01.2022 Accepted: 26.01.2022 Early publication date: 22.02.2022

represents an issue during both immunotherapy and targeted therapy, and there is presently no consensus on the therapeutic journey of patients with *BRAF* mutant melanoma to optimize survival results.

In this review, we will present the molecular features of cutaneous melanoma, focusing on *BRAF* mutation, the therapeutic rationale of targeted therapies, their efficacy, and toxicity, and give an overview of future perspectives in the treatment of this disease.

Molecular features of cutaneous melanoma

Based on the pattern of the most prevalent significant mutated genes in cutaneous melanoma, the Cancer Genome Atlas Network (TCGA) performed a multi-platform characterization of 333 cutaneous melanomas at the DNA, RNA, and protein levels, creating a framework for genomic classification with four subtypes: mutant *BRAF* (with an incidence of 52%), mutant *RAS* (28%), mutant *NF1* (14%), and Triple-wild type [6]. The most common *BRAF* mutation is the V600E, accounting for nearly 90% of mutations, while others are far less common (e.g., V600K, V600D) [7]. Other common genetic alterations found in cutaneous melanoma are *NF1* mutations (15%) and activating mutations of neuroblastoma *RAS* (*NRAS*) (15–30%) [6]. The gain-of-function *BRAF* and *NRAS* and the loss-of-function *NF1* mutations all lead to the constitutive activation of downstream RAS/RAF/MEK/ERK proteins (i.e. the MAPK pathway), which proteins sustain tumor cell proliferation and survival and is a key driver in the pathogenesis of melanoma [8]. However, despite several efforts, no *RAS* inhibitors have yet demonstrated their efficacy in clinical trials [9]. Combinations of BRAF and MEK inhibitors that target the MAPK pathway have been developed. Therefore, only mutations in the $BRAF^{V600}$ gene are therapeutically relevant, while no other valid druggable targets have been identified so far.

Current evidence and future challenges of BRAF and MEK inhibitors

Vemurafenib (PLX4032; trade name: Zelboraf®) was the first molecule to establish the clinical activity of BRAF inhibitors (BRAFi) in *BRAF* mutant melanoma [10]. The BRIM-3 trial was a randomized phase-III clinical trial comparing vemurafenib with dacarbazine in 675 patients with previously untreated $BRAF^{V600E/K}$ mutant metastatic melanoma [11]. The overall response rate (ORR) was 48% and 5%, with vemurafenib and dacarbazine, respectively [11]. Clinical benefit was seen in all enrolled patients, including those with M1c stage and/or the elevated baseline lactate dehydrogenase (LDH) level. Based on the results of this clinical trial, in 2011, vemurafenib was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of $BRAF^{V600}$ mutant advanced melanoma patients. A recently updated analysis of the BRIM-3 trial results showed that Kaplan-Meier estimates of OS rates for vemurafenib *vs.* dacarbazine were 56% *vs.* 46%, 30% *vs.* 24%, 21% *vs.* 19%, and 17% *vs.* 16% at 1, 2, 3 and 4 years, respectively [12].

Dabrafenib (GSK2118436; trade name: Tafinlar®) was the second BRAFi to demonstrate a significantly improved progression-free survival (PFS) in comparison with conventional cytotoxic chemotherapy among patients with $BRAF^{V600E}$ mutant melanoma (5.1 *vs.* 2.7 months for dabrafenib and dacarbazine, respectively) [13]. ORR was 50% and 6% in patients who received dabrafenib and dacarbazine, respectively. Dabrafenib received US FDA approval for the treatment of patients with $BRAF^{V600E}$ mutated melanoma in 2013.

Despite the clinical benefit seen in nearly all patients with *BRAF* mutant melanoma receiving vemurafenib or dabrafenib monotherapy, median PFS lasts only six months and 90% of patients develop resistance within one year from starting treatment [14]. Several acquired molecular mechanisms account for this resistance; however, the most important is the reactivation of the MAPK pathway through alternative activation of downstream MEK [15, 16]. Dual MAPK pathway inhibition with MEK inhibitor (MEKi) plus a BRAFi [17] led to improved efficacy and tolerability of treatment, as reported in the results of Phase-III prospective randomized studies [18–20]. The therapeutic efficacy of the vemurafenib and cobimetinib (GDC-0973; trade name: Cotellic®) combination was first demonstrated in the BRIM-7, open-label, phase-Ib, dose-escalation study [21]. This trial enrolled patients with advanced $BRAF^{V600}$ mutant melanoma who had progressed, or not, on vemurafenib. Treatment consisted of vemurafenib 720 or 960 mg twice a day continuously, and cobimetinib 60, 80, or 100 mg once daily with different schedules of administration (14-days on/14-days off, 21-days on/7-days off, or continuous). The ORR was 87% *vs.* 15%, and PFS was 13.7 and 2.8 months, in vemurafenib naive and pre-treated patients, respectively. Median OS in BRAFi naive population was 31.2 months, and OS at 1, 2, 3, and 4 years was 82.5%, 63.9%, 39.2, and 35.9%, respectively. This study found the safest schedule to be continuous vemurafenib 960 mg twice daily, plus cobimetinib 60 mg daily 21-days on/7-days off, which then became the approved regimen for clinical use.

The subsequent CoBRIM study was the clinical trial that led to the FDA approval of vemurafenib in combination with cobimetinib [18]. In this Phase-III

multicenter trial, patients with previously untreated, locally advanced stage IIIC or IV *BRAF*^{V600} mutant melanoma were randomly assigned to receive vemurafenib plus cobimetinib (n = 247) or vemurafenib plus placebo (n = 248). The ORR was significantly improved with the combination therapy compared to BRAFi alone (70% *vs.* 50%, p < 0.0001). Updated results with an extended follow-up showed that at a median follow-up of 14.2 months, the median PFS was 12.3 for the combination group and 7.2 months for the control group (HR for death or disease progression 0.58, 95% CI 0.46–0.72, p < 0.0001) [22]. Median OS for the combination therapy group was 22.3 months (95% CI, 20.3–not reached) *vs.* 17.4 months (95% CI, 15–19.8) for the monotherapy group (HR 0.70, 95% CI 0.55–0.9, p = 0.005). Combined BRAFi + MEKi confirmed their superiority regardless of baseline prognostic factors, such as the tumor burden or presence of visceral metastases: OS at 1-, 2- and 3-year was 74.5%, 48.3%, and 37.4%, respectively, in the vemurafenib plus cobimetinib group, and 63.8%, 38.0%, and 31.1%, in the control group. Survival results were even better in the subgroup of patients with normal *vs.* elevated LDH levels. A longer PFS was observed with the combination even in patients with *BRAF* ^{V600K} mutant melanoma, which is a rare mutation known to confer less sensibility to BRAFi (HR 0.27) [22].

The pharmacokinetic activity and safety of combined dabrafenib and trametinib (GSK1120212; trade name: Mekinist®) was investigated in an open-label study in 85 *BRAF*^{V600} mutated metastatic melanoma. The same study subsequently randomized 162 patients with *BRAF*^{V600} mutated metastatic melanoma to receive combination therapy with dabrafenib plus trametinib or dabrafenib monotherapy [23]. The median PFS was 9.4 months with the combination *vs.* 5.8 months with monotherapy (HR for progression or death 0.39, 95% CI 0.25–0.62, p < 0.001). The phase-III trial COMBI-d evaluated 423 patients with advanced/metastatic *BRAF*^{V600} mutant melanoma, who were randomly assigned to receive first-line treatment with dabrafenib and trametinib or dabrafenib plus placebo [24]. The ORR was higher with the combination therapy (67 *vs.* 51%, p = 0.002). In the updated analysis, the median duration of progression-free survival was 11.1 months. The PFS rates were 21% at 4, and 19% at 5 years. Patients with a normal baseline lactate dehydrogenase level (at or below the upper limit of the normal range) had a 5-year progression-free survival rate of 25% as compared with 8% in patients with an elevated lactate dehydrogenase level at baseline. In the subgroup of 216 patients with normal LDH levels and fewer than three disease sites at baseline, the 5-year progression-free survival rate was 31% [25]. The median OS duration was 25.9 months, with OS rates of 37% at 4 years, and 34% at 5 years. Similarly, the 5-year OS rate was higher among the patients who had a normal LDH level at baseline than among those with an elevated level (43% *vs.* 16%). The estimated 5-year OS rate was 55% among patients with a normal LDH level and fewer than three organ sites with metastasis at baseline [25]. Importantly, the combination of dabrafenib and trametinib seemed to improve health-related quality of life compared to dabrafenib alone [26].

The efficacy of dabrafenib and trametinib *vs.* vemurafenib alone was evaluated in the phase-III COMBI-v trial [27]. ORR was higher in the dabrafenib plus trametinib arm compared to vemurafenib alone (67 *vs.* 53%, p < 0.001). Median PFS was significantly longer among patients treated with the combination therapy (12.1 *vs.* 7.3 months; HR 0.61, 95% CI 0.51–0.73, p < 0.001); median OS was also improved: 26.1 months and 17.8 months in the combination and monotherapy group, respectively. Consistently, the subgroup of patients with normal baseline LDH levels demonstrated to gain even more benefit from the combination therapy, with a median PFS? of 17.5 months among patients treated with the combination therapy (*vs.* 9.2 months with monotherapy, HR 0.55) while, in the subgroup of patients with elevated LDH levels, median PFS in the combination therapy arm was 5.5 months (*vs.* 4.0 months with monotherapy, HR 0.70). In the subgroup of patients with normal LDH levels, median OS was 21.5 months with vemurafenib alone and median OS was not reached with the combination (HR 0.56) [27]. According to the latest update, the survival benefit was maintained over time: the 2- and 3-year analysis showed that 53 and 45% of patients, respectively, were still alive in the combination therapy group *vs.* 39 and 31% of patients receiving vemurafenib alone [28].

Notably, trametinib was the only MEKi that showed clinical activity as monotherapy in BRAF-mutant melanoma. Based on the results of a phase-II study on BRAFi-naive patients, in which trametinib showed significant clinical activity in patients with *BRAF*-mutant melanoma [29], the phase-III METRIC trial compared first-line treatment with trametinib *vs.* conventional chemotherapy (dacarbazine or paclitaxel) [30]. Patients receiving trametinib demonstrated a higher ORR (22 *vs.* 8%), a longer median PFS (4.8 *vs.* 1.5 months, p < 0.001), and increased 6-month OS (81 *vs.* 67%, HR 0.54, p = 0.01). Based on these results, in 2013, trametinib was approved by US FDA for the treatment of *BRAF* $^{V600E/K}$ mutant melanoma patients not previously exposed to BRAFi.

Recently, a third combination of BRAFi and MEKi has been developed and approved. Combined treatment with encorafenib (LGX818; trade name: Braftovi®) and binimetinib (ARRY-162; trade name: Mektovi®)

extended PFS and reduced the risk of death compared to vemurafenib monotherapy, based on the results of the pivotal two-part, Phase-III randomized COLUMBUS trial [20]. In Part 1, *BRAF*$^{V600E/K}$ mutant metastatic melanoma patients (n = 577) were randomly assigned (1:1:1) to receive encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, or monotherapy with standard-dose vemurafenib, or encorafenib 300 mg once daily. The primary endpoint was the median PFS of the combination *versus* vemurafenib. At the primary analysis (median follow-up: 16.6 months), median PFS was 14.9 months in the combination group, and 7.3 months in the vemurafenib group (HR 0.54, p < 0.0001). ORR was 63% in the combination therapy group, and 40% in the vemurafenib group. At a pre-planned OS analysis, the median OS with encorafenib plus binimetinib was 33.6 months, compared with 16.9 months for vemurafenib alone (HR 0.61, p < 0.0001) [31]. Part 2 of the COLUMBUS trial was conducted upon request of the US FDA, to better understand the contribution of binimetinib in the combination therapy, through comparison of encorafenib 300 mg once daily plus binimetinib 45 mg twice daily *vs.* encorafenib 300 mg daily monotherapy. The second part randomized 344 patients in a 3:1 ratio and is currently ongoing. Preliminary results from a primary analysis of Part 2 showed a longer PFS with combination therapy (n = 258 patients) compared with the encorafenib monotherapy group (i.e. n = 280 patients treated with encorafenib 300 mg in COLUMBUS Parts 1 and 2 combined) [32]. Median PFS was 12.9 *vs.* 9.2 months for the combination and the monotherapy groups, respectively (HR 0.77, p = 0.029) [32]. A five-year update from the Part 1 of the COLUMBUS trial was recently presented, confirming a median OS of 33.6 months and a 5-year OS rate of 34.7% with combination therapy (median follow-up: 70.4 months) [33]. The 5-year OS rate among patients who had normal LDH at baseline and received combination therapy was 45.1%. The 5-year PFS rate for combination therapy, encorafenib monotherapy, and vemurafenib monotherapy was 22.9%, 19.3%, and 10.2%, respectively; ORR was 64.1%, 51.5%, and 40.8%; and the median duration of response (DOR) was 18.6, 15.5, and 12.3 mo, respectively [33].

The four randomized phase-III trials comparing the therapeutic efficacy of the combination of BRAFi and MEKi *vs.* BRAFi alone (COMBI-D, COMBI-V, CoBRIM, and COLUMBUS) showed quite homogeneous data in terms of the response rate (63–70%), OS (median > 24 months), and PFS (median values ranging from 11 to 14 months). The latter reflects the development of resistance mechanisms in the majority of patients. From a molecular point of view, the acquired resistance is related to a re-activation of the MAPK pathway [15–17]. From a clinical point of view, a regression tree analysis identified three independent favorable prognostic factors during treatment with BRAFi plus MEKi: pre-treatment LDH levels, presence of < 3 metastatic sites, and the sum of lesion diameters < 66 mm. In the most favorable prognostic group, 3-year PFS was 42%, suggesting that a low disease burden at baseline can be prognostic for a long-term benefit with targeted therapies [34, 35].

All studies with BRAFi + MEKi continued treatment until disease progression or the onset of unacceptable treatment-related toxicities, which is the standard of care in clinical practice. Experience deriving from small case series in the literature suggests that treatment discontinuation, even after the complete response has been reached, leads to disease recurrence in 50% to 100% of patients [36, 37] and is, therefore, not recommended.

On the contrary, in presence of oligoprogression, targeted therapy can be continued to obtain the best therapeutic results. In retrospective series, it has been reported that the so-called "treatment beyond progression" can increase disease control by adding a loco-regional approach and maintaining the targeted therapy. In a retrospective analysis of 114 patients enrolled in clinical trials, 31% of them progressed in isolated sites [38]. Even after adjusting for potential prognostic factors at progression, continued BRAFi was associated with prolonged OS compared with cessation. In a long-term follow-up analysis of patients treated in the phase-I vemurafenib trial, the median survival was 26.0 months (range, 7.7–56.1) among 20 patients who continued vemurafenib after local therapy [39]. Nevertheless, these retrospective analyses cannot exclude selection biases and different paths of melanoma growth in patients who received (or not) treatment beyond progression.

Table 1 summarizes the outcome and landmark analyses of the available doublet combinations. Currently, the long-term activity and the efficacy of different combo-targeted therapies so far reported seem to be quite similar. Consequently, different toxicity profiles of each combination therapy should drive clinicians in routine activity.

Targeted therapy for the treatment of brain metastases

The activity of dabrafenib as monotherapy and dabrafenib plus trametinib was investigated in melanoma patients with brain metastases. Results from the phase 2 BREAK-MB trial provided evidence that dabrafenib monotherapy exhibits clinical activity and a manageable safety profile in patients with *BRAF*$^{V600E/K}$ mutant melanoma brain metastases, regardless of previous local treatment [40]. The subsequent phase-II COMBI-MB trial investigated the combination of dabrafenib and

Table 1. Overview of the most common adverse events associated with BRAF and MEK inhibitors as monotherapy or in combination in major clinical trials

	Monotherapy				Combination therapy				
Study	**BREAK–3**	**BRIM–3**	**METRIC**	**NEMO**	**BRF112320 (part c)**	**COMBI–d**	**COMBI–v**	**coBRIM**	**COLUMBUS**
Agent(s)	**Dabrafenib**	**Vemurafenib**	**Trametinib**	**Binimetinib**	**Dabrafenib + Trametinib**	**Dabrafenib + Trametinib**	**Dabrafenib + Trametinib**	**Vemurafenib + Cobimetinib**	**Encorafenib + Binimetinib**
Patients (n)	187	336	211	269	55[a]	209	350	247	192
Any AE (%)	–	99	–	–	100	87	98	99	98
Grade 3–4 AEs	–	71	–	–	58	32	48	75	58
Most common AEs (≥ 20% incidence), any grade/grade 3–4(%)									
Pyrexia	33/4	21/< 1	–	10/0	71/5	52/7	53/4	29/1	16/4
Chills	12/0	7/0	–	–	58/2	28/0	31/1	–	–
Fatigue	26/2	46/3	26/4	20/2	53/4	27/2	29/1	37/4	27/2
Nausea	29/< 1	38/2	18/1	28/1	44/2	20/0	35/< 1	42/1	42/2
Vomiting	22/2	21/2	13/1	19/2	40/2	14/< 1	29/1	25/2	30/2
Diarrhea	17/1	36/1	43/0	39/1	36/2	18/< 1	32/1	61/6	35/2
Arthralgia	39/2	56/6	–	–	27/0	16/< 1	24/1	38/2	27/1
Headache	36/0	33/1	–	–	29/0	19/0	29/< 1	–	23/2
Rash	19/0	41/9	57/8	32/4	27/0	24/0	22/1	72/17[b]	27/2[b]
Cough	18/0	13/0	–	–	29/0	–	20/0	–	12/1
Peripheral edema	–	20/< 1	26/1	36/< 1	29/0	11/1	12/< 1	–	10/2
Decreased appetite	13/0	22/< 1	–	11/1	22/0	–	12/< 1	–	9/0
Pruritus	–	25/1	10/2	11/1	–	7/0	9/0	–	12/1
Acneiform dermatitis	–	5/0	19/< 1	33/3	16/0	8/0	6/0	–	–
Alopecia	29/< 1	48/0	17/< 1	–	5/0	5/0	6/0	17/< 1	14/0
Constipation	14/2	14/< 1	14/0	13/1	22/0	–	13/0	–	24/0
Asthenia	20/< 1	14/< 1	–	15/3	–	–	16/1	–	19/2

→

Table 1 cd. Overview of the most common adverse events associated with BRAF and MEK inhibitors as monotherapy or in combination in major clinical trials

	Monotherapy				Combination therapy				
Study	**BREAK–3**	**BRIM–3**	**METRIC**	**NEMO**	**BRF112320 (part c)**	**COMBI–d**	**COMBI–v**	**coBRIM**	**COLUMBUS**
Myalgia	17/0	15/1	–	–	22/2	–	–	–	16/0
Photosensitivity reaction	3/0	41/4	–	–	–	–	4/0	48/4	3/1
cuSCC/KA	12/7	30/29	0	–	7/5	3/3	1/1	6/5	3/1
Dry skin	13/0	23/0	11/0	–	–	9/0	8/0	–	16/0
Hyperkeratosis	41/2[c]	29/1	–	–	9/0	6/0	4/0	10/< 1	15/1
Hand foot syndrome/PPE	20/2	9/< 1	–	–	–	6/< 1	4/0	–	16/0
Skin papilloma	26/0	28/< 1	–	–	4/0	1/0	2/0	–	8/0
Hypertension	–	3/1	15/12	6/7	9/2	–	26/14	–	8/6
Increased ALT	–	8/2	–	6/3	–	10/2	14/3	26/11	6/5
Increased AST	–	7/< 1	–	11/2	11/3	11/1	11/1	24/9	7/2
Increased creatine kinase	–	7/< 1	–	23/19	–	–	–	35/12	18/8
Increased γ-GT	–	–	–	2/1	–	–	–	22/15	6/9
Serous retinopathy[d]	–	–	–	–	2/2	< 1/0	1/0	27/3	–

[a]Data for dosage arm of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily; [b]Combined terms include the preferred terms rash, rash maculopapular, erythema, dermatitis acneiform, folliculitis, rash macular, rash papular, rash erythematous, acne, dermatitis, rash pruritic, furuncle, rash generalized, dermatitis allergic, rash follicular, rash pustular, dermatitis exfoliative, generalized erythema, rash morbilliform, and drug eruption; [c]Hyperkeratosis included acanthoma, acrochordon, actinic keratosis, keratosis pilaris, lichenoid keratosis, papilloma, seborrheic keratosis, and skin papilloma; [d]Combined terms include the preferred terms chorioretinopathy, retinal detachment, detachment of retinal pigment epithelium, macular oedema, macular fibrosis, retinal disorder, retinopathy, subretinal fluid, and detachment of macular retinal pigment epithelium; AE — adverse event; ALT — alanine aminotransferase; AST — aspartate aminotransferase; cuSCC — cutaneous squamous cell carcinoma; γ-GT — gamma-glutamiltransferase; KA — keratoacanthoma; PPE — palmar-plantar erythrodysesthesia

trametinib in four melanoma patient cohorts: (A) *BRAF*^{V600E}, asymptomatic, no prior local brain therapy; (B) *BRAF*^{V600E}, asymptomatic, prior local brain therapy; (C) *BRAF*$^{V600D/K/R}$, asymptomatic, with or without prior local brain therapy; and (D) *BRAF*$^{V600D/E/K/R}$, symptomatic, with or without prior local brain therapy [41]. The primary endpoint was intracranial response rate (IRR), and it was met only in cohort A (IRR 58%). Intracranial responses were observed also in cohorts B, C, and D (IRR 56, 44, and 59%, respectively), but due to the small sample sizes of these cohorts, these findings should be considered exploratory. The median duration of response was relatively short, between 4.2 and 7.2 months [41].

Data from the phase-II trial GEM1802/EBRAIN-MEL, evaluating the combination of encorafenib and binimetinib among two different cohorts of patients with brain metastases (i.e., patients with symptoms and those asymptomatic) showed that this combination provided intracranial response rate of 64.3% and 63.6% in the two patients cohorts, thus supporting clinical activity of targeted therapy regardless of the presence of symptoms [42].

Safety profile and toxicity of BRAFis and MEKis

BRAFis and MEKis display peculiar adverse events (AEs), which are similar in the two classes of drugs while some are specific to a particular drug. Both on-target and off-target AEs have been reported, with on-target AEs being related to the paradoxically hyper-activation of the MAPK pathway. Most AEs are milder with the combination of the two agents, while others exacerbate. Since targeted therapy is taken chronically until disease progression or unacceptable toxicity, prompt identification and treatment of AEs and preservation of quality of life (QoL) are important goals in patients' management [43].

The safety profile of BRAFi and MEKi drugs has been well characterized both in clinical trials and routine clinical practice. The highest rates of AEs seem to occur early in treatment and their incidence decreases over time [43]. Most AEs are mild [i.e. grade 1–2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03], transient, and easily manageable with treatment withdrawal, without requiring dose adjustments. In studies with combination treatment, the incidence of dose reduction or interruption due to AEs range between 11–58% and 46–67%, respectively, while the percentage of patients permanently discontinuing treatment due to AEs was 11–14%. Importantly, BRAFi- and MEKi-related AEs usually resolve with therapy withdrawal and late toxicities are uncommon after drug discontinuation [43].

Each combination displays a peculiar profile of AEs, though most of them are similar and their prevalence varies according to the specific combination. Table 2 summarizes the incidence of AEs reported in the major clinical trials of mono- and combo-targeted therapy. The most common AEs during treatment with vemurafenib and cobimetinib were gastrointestinal (GI) events (i.e. diarrhea, nausea, and vomiting), cutaneous rash, fatigue, pyrexia, arthralgia, photosensitivity reactions, increased creatinine kinase (CK) levels, and altered liver function tests (LFT). Some of those AEs had an increased incidence in the case of the combination compared with BRAFi monotherapy (e.g. GI events, photosensitivity reactions, and altered LFTs). Similarly, combination therapy was characterized by a higher incidence of MEKi-related AEs, such as elevated CK levels and ocular events. Ocular toxicity depends on the inflammatory response and breakdown of the blood-retinal barrier brought driven by MAPK pathway inhibition. AEs can range from mild visual impairment and decreased visual function to more serious uveitis, retinal epithelial detachment, and retinal vein occlusion. The latter effect generally implies the permanent discontinuation of

Table 2. Overview and comparison of the major characteristics of clinical trials of combination targeted therapy for melanoma

Clinical study (reference)	ORR	Median PFS	Median OS	OS (%)			≥ 3 met. sites	LDH > ULN	I-O post	Discontinuation
				1 yr	2 yrs	3 yrs				
COBRIM	70%	12.3	22.3	75%	48%	–	–	46%	18%	16.6%
COMBI-d	68%	11.0	25.1	74%	52%	44%	48%	36%	20%	14%
COMBI-v	67%	12.1	26.1	72%	53%	45%	50%	34%	9%	16%
COLUMBUS	76% 64% BIRC	14.9	33.6	75.5%	57.6%		45%	29%	20%	15% 6% drug related

BIRC — Blinded Independent Review Committee; LDH — lactate dehydrogenase; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; ULN — upper limit of normal

treatment. However, most ocular events are transient and self-limiting and either resolve with dose reduction or temporary drug interruption [44]. Combination therapy had a lower incidence of hyperproliferative cutaneous lesions, which were commonly observed with vemurafenib monotherapy [18, 21–22]. This type of skin toxicity, affecting virtually all patients receiving BRAFi monotherapy, results from the paradoxical activation of the MAPK pathway leading to subsequent keratinocyte hyperproliferation and development of cutaneous squamous cell carcinoma (SCC), verrucal keratosis, and plantar hyperkeratosis [45]. Data from a specific analysis of the characteristics and patterns of AEs in the coBRIM trial indicate that most treatment-related AEs generally occur early in the treatment course, are mild to moderate, and are manageable by patient monitoring, dose modification, and supportive care [43].

The safety profile of dabrafenib and trametinib was evaluated in three clinical trials [19, 24, 27]. The most common AEs were pyrexia, chills, fatigue, headache, GI events (nausea, diarrhea), arthralgia, cutaneous rash, and hypertension. Pyrexia, in particular, was one of the leading reasons for dose modification, treatment interruption, and permanent withdrawal [24]. Also, for dabrafenib and trametinib, MEKi related AEs (i.e. peripheral edema, decreased left ventricular ejection fraction [LVEF], and acneiform dermatitis) were most common with the combination therapy, while hyperproliferative skin lesions were less commonly observed [24].

Data regarding the safety of encorafenib and binimetinib suggest that it might overcome other combination therapies for its tolerability. The most-reported AEs in part I of the COLUMBUS trial were GI events, fatigue, increased CK, and headache [31]. The incidence and severity of pyrexia were much lower than with dabrafenib and trametinib. In the COLUMBUS trial, pyrexia with encorafenib and binimetinib was low in frequency (18%) with few grade 3 events (4%) and resulted in few dose modifications or discontinuations. The majority of the higher grade of adverse events were associated with concurrent infection or progression of the disease. Furthermore, photosensitivity was rarely observed.

Data from phase-III trials suggest that most AEs are manageable with temporary drug interruption, while only intolerable AEs require dose modification and/or discontinuation. Usually, the drug that is most likely associated with an AE should be interrupted and/or reduced. To optimize clinical response while preserving QoL, early detection and management of treatment-related AEs are of paramount importance. Reports from case series of patients interrupting treatment with BRAFi and MEKi because of AEs onset after reaching complete response show that almost half of those patients eventually relapse [36, 37, 46, 47]. Even if most of these patients seem to gain benefit from treatment rechallenge [47, 48], this suggests that therapy continuation should be pursued whenever possible, even in those patients showing complete response to treatment. Notably, there is strong evidence that global health and most functional and symptom domain scores improve significantly in favor of the combination therapy group compared with BRAFi alone [49–51].

Finally, to optimize the efficacy and the different spectrum of toxicity with targeted therapy and immunotherapy, clinical trials are currently underway to elucidate whether sequential and/or interrupting administration of BRAFi and MEKi, also in combination with different treatment approaches (mainly immunotherapy), could optimize disease response and outcomes (see further section).

Perspectives

The combination of BRAFi and MEKi has revolutionized the treatment of patients with metastatic melanoma. However, despite the unquestionable improvement in the response rate and disease control obtained with combined targeted therapies, acquired resistance eventually develops in more than half of patients after approximately 12 months from the beginning of treatment [51]. Significant efforts are ongoing to understand how to obtain the best response by combining BRAFi and MEKi and how to sequence or combine targeted therapy with ICIs. Most importantly, biomarkers and/or clinical features should be identified to select patients with BRAF mutant disease who can benefit more from BRAFi plus MEKi and those who could obtain better disease control with a planned sequence or an upfront combination of ICIs in association with BRAFi and MEKi.

There is plenty of evidence that BRAFi and MEKi have immune-modulatory properties [52]. BRAFi can downregulate immunosuppressive cytokines, decrease the recruitment of regulatory T cells (T regs) and myeloid-derived stem cells (MDSCs), and increase major histocompatibility complex (MHC) class I and antigen expression. Blocking the MAPK pathway in *in vitro* cell lines leads to an increased antigen expression and enhanced reactivity to antigen-specific T lymphocytes [53]. Although in *in vitro* experiments, MEKis may promote a T cell suppressive microenvironment [54, 55], in tumor biopsies from melanoma patients receiving BRAFi and MEKi (either alone or in combination), there is evidence that blocking two steps in the MAPK signaling, the effects are similar on the immunosuppressive microenvironment [55–57].

Despite promising preliminary results, however, most clinical trials investigating the combination of ICIs with targeted therapy failed to demonstrate a signifi-

cant improvement in terms of ORR and survival rate for the triple combination, at the expense of increased toxicity [58, 59]. The only phase-III trial demonstrating a superior PFS for the combination of ICIs and targeted therapy was the IMspire150. In this randomized trial, 514 patients with unresectable stage IIIc-IV, $BRAF^{V600}$ mutation-positive melanoma were randomly assigned 1:1 to atezolizumab, vemurafenib, and cobimetinib or atezolizumab placebo, vemurafenib, and cobimetinib (the control group) [60]. At a median follow-up of 18.9 months, PFS was significantly prolonged with atezolizumab *versus* control (15.1 *vs.* 10.6 months; p = 0.025). The most common treatment-related AEs in the atezolizumab and control groups were increased blood CPK (51.3% *vs.* 44.8%), diarrhoea (42.2% *vs.* 46.6%), rash (40.9%, both groups), arthralgia (39.1% *vs.* 28.1%), pyrexia (38.7% *vs.* 26.0%), increased alanine aminotransferase (33.9% *vs.* 22.8%), and increased lipase (32.2% *vs.* 27.4%). Overall, 13% of patients in the atezolizumab group and 16% in the control group stopped study treatment because of adverse events [60].

In the context of combining targeted therapy with immunotherapies, phase I and I/II studies are investigating the combination of BRAFi + MEKi with new molecules, like heat shock protein 90 inhibitor (Hsp90i) (NCT02721459), colony-stimulating factor 1-receptor inhibitor (CSF-1Ri) (NCT 03101254), and cytokines like IFN and IL-2. Further innovative strategies include the combination of standard therapies (namely BRAFi and chemotherapy) with adoptive cell transfer (ACT) and/or tumor-infiltrating lymphocytes (TIL). Given that such combinations may not be suitable for all patients, in terms of toxicities but also of increased costs, clinical trials are investigating the best sequential regimens of BRAFi + MEKi and ICIs. The rationale behind sequential strategies lies in different kinetics of response between combo-targeted therapy and immunotherapy. Patients with baseline unfavorable prognostic factors (i.e. elevated serum LDH, high tumor burden) are less likely to respond to upfront immunotherapy but could benefit from immunotherapy once LDH levels are normalized and the tumor burden reduced with BRAFi + MEKi-based induction treatment. The SECOMBIT study, a randomized three-arm phase-II study with no formal comparative test (NCT02631447), was started to investigate the best sequential strategy of treatment for patients with BRAF mutant melanoma. In this study, 251 patients were randomized to Arm A (encorafenib plus binimetinib until progressive disease, followed by ipilimumab and nivolumab until progressive disease), or Arm B (ipilimumab and nivolumab until progressive disease, followed by encorafenib plus binimetinib until progressive disease), or Arm C (encorafenib plus binimetinib for 8 weeks, followed by ipilimumab and nivolumab until progressive disease, followed by encorafenib plus binimetinib until progressive disease) [61]. The study primary endpoint of OS was met in each arm; the median OS was not reached in any of the treatment arms. The survival rate at 2 and 3 years was 65% and 54% in arm A, 73% and 62% in arm B, and 69% and 60% in arm C, respectively. Total PFS rate at 2 and 3 years was 46% and 41% in arm A, 65% and 53% in arm B, 57% and 54% in arm C.

Similarly, the DREAMseq study randomized 265 patients with treatment-naïve BRAF V600 positive metastatic melanoma to receive step I treatment with nivolumab plus ipilimumab (arm A) or dabrafenib plus trametinib (arm B). Upon disease progression, patients were enrolled in step II of the trial: patients in arm A switched over to dabrafenib plus trametinib, while patients in arm B switched to nivolumab plus ipilimumab [62]. At a median follow-up of 27.7 months, PFS showed a trend (p = 0.054) favoring patients in arm A. As for OS, a 20% difference in survival was observed (p = 0.0095) at the 2-year time point (72% and 52% for arm A and arm B, respectively) [62]. Even though these preliminary data are interesting, results from these two studies do not consent to do derive significant recommendations to be used in the clinical practice.

Another interesting strategy to synergize the effect of BRAFi +/- MEKi is represented by inhibition of the cyclin-dependent kinase (CDK) 4–6, which is a highly dysregulated pathway in melanoma. Evidence from *in vitro* and *in vivo* studies of the upfront combination of the CDK 4/6 inhibitor palbociclib in combination with BRAFi and/or MEKi seem to evade cell resistance and induce sustained tumor regression [63, 64]. Moreover, co-targeting of MEK and CDK 4/6 seems to have therapeutic effects in a subset of cutaneous melanoma regardless of their mutational status (i.e. NRAS, BRAF mutant, as well as wild-type melanomas) [65]. The use of CDK 4/6 inhibitors in combination with BRAFi and/or MEKi is currently under investigation in ongoing clinical trials [66].

Future clinical trials will include a consistent body of translational research (baseline tissue and plasma samples, with analysis of their dynamic changes during treatment) that will help identify which patients are more likely to gain long-term benefit from sequential or combined targeted and immune therapy.

Conclusions

In the last decade, the medical oncology community has witnessed a dramatic paradigm shift in the treatment of metastatic melanoma. Targeted therapy with BRAFi and MEKi has provided undoubted therapeutic improvement for BRAF mutant disease. However, patients' selection and the onset of acquired resistance during treatment are still problematic. One of the most

fascinating fields of the investigation remains how to integrate immunotherapy with targeted therapies in *BRAF* mutated melanoma patients. There is, indeed, strong evidence now supporting the notion that the therapeutic efficacy of BRAFi and MEKi relies on other factors including the immunomodulation of the microenvironment. Nevertheless, several unanswered questions remain, mostly regarding potential therapeutic combinations and treatment sequencing. Prospective clinical trials are needed to identify the best therapeutic strategy for the treatment of BRAF mutant melanoma and to further improve therapeutic results in this setting.

Conflict of interest

None to declare.

References

1. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27(36): 6199–6206, doi: 10.1200/JCO.2009.23.4799, indexed in Pubmed: 19917835.
2. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363(8): 711–723, doi: 10.1056/NEJMoa1003466, indexed in Pubmed: 20525992.
3. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015; 16(4): 375–384, doi: 10.1016/S1470-2045(15)70076-8, indexed in Pubmed: 25795410.
4. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015; 16(8): 908–918, doi: 10.1016/S1470-2045(15)00083-2, indexed in Pubmed: 26115796.
5. Tsao H, Chin L, Garraway LA, et al. Melanoma: from mutations to medicine. Genes Dev. 2012; 26(11): 1131–1155, doi: 10.1101/gad.191999.112, indexed in Pubmed: 22661227.
6. Rajkumar S, Watson IR. Cancer Genome Atlas Network. Genomic Classification of Cutaneous Melanoma. Cell. 2015; 161(7): 1681–1696, doi: 10.1016/j.cell.2015.05.044, indexed in Pubmed: 26091043.
7. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. Cell. 2012; 150(2): 251–263, doi: 10.1016/j.cell.2012.06.024, indexed in Pubmed: 22817889.
8. Farooq A, Zhou MM. Structure and regulation of MAPK phosphatases. Cell Signal. 2004; 16(7): 769–779, doi: 10.1016/j.cellsig.2003.12.008, indexed in Pubmed: 15115656.
9. Samatar AA, Poulikakos PI. Targeting RAS-ERK signalling in cancer: promises and challenges. Nat Rev Drug Discov. 2014; 13(12): 928–942, doi: 10.1038/nrd4281, indexed in Pubmed: 25435214.
10. Chapman PB, Hauschild A, Robert C, et al. BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364(26): 2507–2516, doi: 10.1056/NEJMoa1103782, indexed in Pubmed: 21639808.
11. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014; 15(3): 323–332, doi: 10.1016/S1470-2045(14)70012-9, indexed in Pubmed: 24508103.
12. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol. 2017; 28(10): 2581–2587, doi: 10.1093/annonc/mdx339, indexed in Pubmed: 28961848.
13. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380(9839): 358–365, doi: 10.1016/S0140-6736(12)60868-X, indexed in Pubmed: 22735384.
14. Zhao Y, Adjei AA. The clinical development of MEK inhibitors. Nat Rev Clin Oncol. 2014; 11(7): 385–400, doi: 10.1038/nrclinonc.2014.83, indexed in Pubmed: 24840079.
15. Lito P, Rosen N, Solit D. Tumor adaptation and resistance to RAF inhibitors. Nat Med. 2013; 19(11): 1401–1409, doi: 10.1038/nm.3392.
16. Trunzer K, Pavlick AC, Schuchter L, et al. Pharmacodynamic effects and mechanisms of resistance to vemurafenib in patients with metastatic melanoma. J Clin Oncol. 2013; 31(14): 1767–1774, doi: 10.1200/JCO.2012.44.7888, indexed in Pubmed: 23569304.
17. Villanueva J, Vultur A, Lee JT, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell. 2010; 18(6): 683–695, doi: 10.1016/j.ccr.2010.11.023, indexed in Pubmed: 21156289.
18. Wongchenko MJ, McArthur GA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014; 371(20): 1867–1876, doi: 10.1056/NEJMoa1408868, indexed in Pubmed: 25265494.
19. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015; 386(9992): 444–451, doi: 10.1016/S0140-6736(15)60898-4, indexed in Pubmed: 26037941.
20. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018; 19(5): 603–615, doi: 10.1016/S1470-2045(18)30142-6, indexed in Pubmed: 29573941.
21. Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAFV600-mutated melanoma: a phase 1b study. Lancet Oncol. 2014; 15(9): 954–965, doi: 10.1016/s1470-2045(14)70301-8.
22. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016; 17(9): 1248–1260, doi: 10.1016/S1470-2045(16)30122-X, indexed in Pubmed: 27480103.
23. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012; 367(18): 1694–1703, doi: 10.1056/NEJMoa1210093, indexed in Pubmed: 23020132.
24. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014; 371(20): 1877–1888, doi: 10.1056/NEJMoa1406037, indexed in Pubmed: 25265492.
25. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019; 381(7): 626–636, doi: 10.1056/NEJMoa1904059, indexed in Pubmed: 31166680.
26. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017; 28(7): 1631–1639, doi: 10.1093/annonc/mdx176, indexed in Pubmed: 28475671.
27. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015; 372(1): 30–39, doi: 10.1056/NEJMoa1412690, indexed in Pubmed: 25399551.
28. Robert C, Karaszewska B, Schachter J, et al. Three-year estimate of overall survival in COMBI-v, a randomized phase 3 study evaluating first-line dabrafenib (D) + trametinib (T) in patients (pts) with unresectable or metastatic BRAF V600E/K–mutant cutaneous melanoma. Ann Oncol. 2016; 27: vi575, doi: 10.1093/annonc/mdw435.37.
29. Kim KB, Kefford R, Pavlick AC, et al. Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol. 2013; 31(4): 482–489, doi: 10.1200/JCO.2012.43.5966, indexed in Pubmed: 23248257.
30. Flaherty KT, Robert C, Hersey P, et al. METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012; 367(2): 107–114, doi: 10.1056/NEJMoa1203421, indexed in Pubmed: 22663011.
31. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018; 19(5): 603–615, doi: 10.1016/S1470-2045(18)30142-6, indexed in Pubmed: 29573941.
32. Dummer R, Ascierto PA, Gogas H, et al. Results of COLUMBUS Part 2: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus ENCO in BRAF-mutant melanoma. Ann Oncol. 2017; 28: v429–v430, doi: 10.1093/annonc/mdx377.002.

33. Dummer R, Flaherty K, Robert C, et al. Five-year overall survival (OS) in COLUMBUS: A randomized phase 3 trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients (pts) with BRAF V600--mutant melanoma. J Clin Oncol. 2021; 39(15_suppl): 9507–9507, doi: 10.1200/jco.2021.39.15_suppl.9507.
34. Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol. 2016; 17(12): 1743–1754, doi: 10.1016/S1470-2045(16)30578-2, indexed in Pubmed: 27864013.
35. Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer. 2017; 82: 45–55, doi: 10.1016/j.ejca.2017.05.033, indexed in Pubmed: 28648698.
36. Carlino MS, Vanella V, Girgis C, et al. Cessation of targeted therapy after a complete response in BRAF-mutant advanced melanoma: a case series. Br J Cancer. 2016; 115(11): 1280–1284, doi: 10.1038/bjc.2016.321, indexed in Pubmed: 27711085.
37. Desvignes C, Abi Rached H, Templier C, et al. BRAF inhibitor discontinuation and rechallenge in advanced melanoma patients with a complete initial treatment response. Melanoma Res. 2017; 27(3): 281–287, doi: 10.1097/CMR.0000000000000350, indexed in Pubmed: 28240681.
38. Chan MMK, Haydu LE, Menzies AM, et al. The nature and management of metastatic melanoma after progression on BRAF inhibitors: effects of extended BRAF inhibition. Cancer. 2014; 120(20): 3142–3153, doi: 10.1002/cncr.28851, indexed in Pubmed: 24985732.
39. Puzanov I, Amaravadi RK, McArthur GA, et al. Long-term outcome in BRAF(V600E) melanoma patients treated with vemurafenib: Patterns of disease progression and clinical management of limited progression. Eur J Cancer. 2015; 51(11): 1435–1443, doi: 10.1016/j.ejca.2015.04.010, indexed in Pubmed: 25980594.
40. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK--MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012; 13(11): 1087–1095, doi: 10.1016/S1470-2045(12)70431-X, indexed in Pubmed: 23051966.
41. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAF-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017; 18(7): 863–873, doi: 10.1016/S1470-2045(17)30429-1, indexed in Pubmed: 28592387.
42. Marquez-Rodas I, Arance A, Guerrero MAB, et al. 1038MO Intracranial activity of encorafenib and binimetinib followed by radiotherapy in patients with BRAF mutated melanoma and brain metastasis: Preliminary results of the GEM1802/EBRAIN-MEL phase II clinical trial. Ann Oncol. 2021; 32: S870, doi: 10.1016/j.annonc.2021.08.1423.
43. Dréno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol. 2017; 28(5): 1137–1144, doi: 10.1093/annonc/mdx040, indexed in Pubmed: 28444112.
44. Urner-Bloch U, Urner M, Jaberg-Bentele N, et al. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol. 2014; 25(7): 1437–1441, doi: 10.1093/annonc/mdu169, indexed in Pubmed: 24864047.
45. Carlos G, Anforth R, Clements A, et al. Cutaneous Toxic Effects of BRAF Inhibitors Alone and in Combination With MEK Inhibitors for Metastatic Melanoma. JAMA Dermatol. 2015; 151(10): 1103–1109, doi: 10.1001/jamadermatol.2015.1745, indexed in Pubmed: 26200476.
46. Tolk H, Satzger I, Mohr P, et al. Complete remission of metastatic melanoma upon BRAF inhibitor treatment - what happens after discontinuation? Melanoma Res. 2015; 25(4): 362–366, doi: 10.1097/CMR.0000000000000169, indexed in Pubmed: 26061438.
47. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAF-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol. 2017; 18(4): 464–472, doi: 10.1016/S1470-2045(17)30171-7, indexed in Pubmed: 28268064.
48. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: A multi-institutional retrospective study. Eur J Cancer. 2018; 91: 116–124, doi: 10.1016/j.ejca.2017.12.007, indexed in Pubmed: 29360604.
49. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol. 2015; 16(13): 1389–1398, doi: 10.1016/S1470-2045(15)00087-X, indexed in Pubmed: 26433819.
50. Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015; 51(7): 833–840, doi: 10.1016/j.ejca.2015.03.004, indexed in Pubmed: 25794603.
51. Rizos H, Menzies AM, Pupo GM, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: spectrum and clinical impact. Clin Cancer Res. 2014; 20(7): 1965–1977, doi: 10.1158/1078-0432.CCR-13-3122, indexed in Pubmed: 24463458.
52. Mandalà M, De Logu F, Merelli B, et al. Immunomodulating property of MAPK inhibitors: from translational knowledge to clinical implementation. Lab Invest. 2017; 97(2): 166–175, doi: 10.1038/labinvest.2016.132, indexed in Pubmed: 27991907.
53. Boni A, Cogdill AP, Dang P, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. Cancer Res. 2010; 70(13): 5213–5219, doi: 10.1158/0008-5472.CAN-10-0118, indexed in Pubmed: 20551059.
54. Ott PA, Henry T, Baranda SJ, et al. Inhibition of both BRAF and MEK in BRAF(V600E) mutant melanoma restores compromised dendritic cell (DC) function while having differential direct effects on DC properties. Cancer Immunol Immunother. 2013; 62(4): 811–822, doi: 10.1007/s00262-012-1389-z, indexed in Pubmed: 23306863.
55. Wilmott JS, Long GV, Howle JR, et al. Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012; 18(5): 1386–1394, doi: 10.1158/1078-0432.CCR-11-2479, indexed in Pubmed: 22156613.
56. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res. 2013; 19(5): 1225–1231, doi: 10.1158/1078-0432.CCR-12-1630, indexed in Pubmed: 23307859.
57. Kakavand H, Wilmott JS, Menzies AM, et al. PD-L1 Expression and Tumor-Infiltrating Lymphocytes Define Different Subsets of MAPK Inhibitor-Treated Melanoma Patients. Clin Cancer Res. 2015; 21(14): 3140–3148, doi: 10.1158/1078-0432.CCR-14-2023, indexed in Pubmed: 25609064.
58. Ferrucci PF, Di Giacomo AM, Del Vecchio M, et al. KEYNOTE-022 international team. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in -mutant melanoma. J Immunother Cancer. 2020; 8(2), doi: 10.1136/jitc-2020-001806, indexed in Pubmed: 33361337.
59. Dummer R, Long GV, Robert C, et al. Randomized Phase III Trial Evaluating Spartalizumab Plus Dabrafenib and Trametinib for V600--Mutant Unresectable or Metastatic Melanoma. J Clin Oncol. 2022 [Epub ahead of print]: JCO2101601, doi: 10.1200/JCO.21.01601, indexed in Pubmed: 35030011.
60. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020; 395(10240): 1835–1844, doi: 10.1016/S0140--6736(20)30934-X, indexed in Pubmed: 32534646.
61. Ascierto PA, Mandala M, Ferrucci PF, et al. LBA40 SECOMBIT: The best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma: A phase II randomized study. Ann Oncol. 2021; 32: S1316–S1317, doi: 10.1016/j.annonc.2021.08.2118.
62. Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq: A phase III trial – ECOG Acrin ECOG-ACRIN EA6134. ASCO Plenary Series. Abstract 356154. Presented November 16, 2021.
63. Martin CA, Cullinane C, Kirby L, et al. Palbociclib synergizes with BRAF and MEK inhibitors in treatment naïve melanoma but not after the development of BRAF inhibitor resistance. Int J Cancer. 2018; 142(10): 2139–2152, doi: 10.1002/ijc.31220, indexed in Pubmed: 29243224.
64. Lee B, McArthur GA. CDK4 inhibitors an emerging strategy for the treatment of melanoma. Melanoma Manag. 2015; 2(3): 255–266, doi: 10.2217/mmt.15.14, indexed in Pubmed: 30190853.
65. Posch C, Sanlorenzo M, Ma J, et al. MEK/CDK4,6 co-targeting is effective in a subset of NRAS, BRAF and 'wild type' melanomas. Oncotarget. 2018; 9(79): 34990–34995, doi: 10.18632/oncotarget.26204, indexed in Pubmed: 30405888.
66. Taylor M, Sosman J, Gonzalez R, et al. Phase Ib/Ii Study of Lee011 (Cdk4/6 Inhibitor) and Lgx818 (Braf Inhibitor) in Braf-Mutant Melanoma. Ann Oncol. 2014; 25: iv374, doi: 10.1093/annonc/mdu344.2.

Piotr Rutkowski, Katarzyna Kozak

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Commentary to

Targeted therapy for advanced cutaneous melanoma

The review article "Targeted therapy for advanced cutaneous melanoma" prepared by an expert team from Italy presents in detail current possibilities of therapy for patients with advanced melanoma with the use of molecular targeted agents. During the last decade, the unprecedented development in melanoma treatment is mainly related to the introduction of two different therapeutic strategies: nonspecific immunotherapy using monoclonal antibodies anti-CTLA4 or anti-PD1 (immune checkpoint inhibitors) and targeted therapy with serine-threonine kinases inhibitors. These advances in targeted therapy are related mainly to blockade of the signal pathway of mitogen-activated protein kinases (MAPK), which is overactivated due to mutation in the *BRAF* gene in approximately 50% of melanoma patients [1]. The use of BRAF inhibitor in *BRAF*-mutated melanoma patients allowed for objective responses in about half of patients, which was related to improvement in progression-free survival and overall survival. Further development of targeted therapies led to the introduction of the second inhibitor of the MAPK pathway — MEK inhibitor. This dual blockade was more effective in maintaining a similar safety profile. The development of immunotherapy, especially implementation in clinical practice a combination of nivolumab and ipilimumab, resulted in a scenario in which BRAF/MEK inhibitors are usually used after immunotherapy failure [2]. It is associated with the mechanism of action of immunotherapy enabling, in many patients, long-term disease remissions. Nowadays, research focuses on combined therapies, i.e. combination of kinase inhibitors with immunotherapy and sequential therapy for optimal management of patients with *BRAF*-mutated advanced melanoma because therapy with BRAF inhibitors in monotherapy or in combination with MEK inhibitors increases expression of cancer antigens, lymphocyte T CD8+ infiltrates, and PD-L-1 expression [3].

The results of recent studies (COMBI-d, COMBI-v, coBRIM, and COLUMBUS) showed that in patients with metastatic melanomas with *BRAF* mutation, the use of a combination of BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib with cobimetinib or encorafenib with binimetinib) yields better results than monotherapy with no increase in toxicity [4–6]. The median overall survival time on the combination of both drugs was improved to about 23–33 months and a median progression-free survival to 12–14 months. Better survival is achieved in patients with normal LDH activity and serum concentration and less than three organs involved in metastases. All these two combinations are currently accessible in Poland in the Drug Program B.59 in any line of therapy in patients with advanced melanoma with confirmed presence of $BRAF^{V600}$ mutation, change of one combination into another in case of intolerance, and reintroduction of therapy with kinase inhibitors in subsequent lines of therapy. The above-mentioned drugs have a beneficial influence also in patients with stable and/or asymptomatic metastases to the brain.

A new option of the molecularly targeted therapy is to rechallenge the combined therapy with BRAF and MEK inhibitors after this therapy has been stopped due to disease progression. A phase-II study revealed that restarting therapy with dabrafenib and trametinib resulted in partial remission in eight of 25 patients (32%) and stabilization of the disease in another 40% of patients. The median disease progression-free time after

Received: 25.02.2022 Accepted: 25.02.2022 Early publication date: 03.03.2022

Oncology in Clinical Practice, DOI: 10.5603/OCP.2022.0010, Copyright © 2022 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

reintroduction reached 4.9 months [7]. The similar are results of analysis of data of 116 patients with advanced melanoma, who had received therapy with BRAF inhibitor, progressed, and received another therapeutic modality, and then were restarted on combined therapy with BRAF ± MEK inhibitor. The median time of treatment duration was 9.4 and 7.7 months for the primary and reused molecularly targeted therapy, respectively. After restarting the use of BRAF ± MEK inhibitors the response rate was 43%: complete response rate 3%, partial response rate 39%, stabilization of the disease 24%, and progression of the disease 30% (no data 4%). The median overall survival time from the restart of the therapy reached 9.8 months [8, 9].

There is no final data on the optimal sequence of immunotherapy and targeted therapy in patients with *BRAF* mutation. The activity of BRAF inhibitor is maintained after immunotherapy and of immunotherapy (anti-PD-L1) after treatment with BRAF inhibitors BRAF inhibitors [10]. The results of SECOMBIT and DREAMseq trials indicate that the combination of nivolumab and ipilimumab gives the best outcomes if used as the first-line option in patients with advanced *BRAF*-positive melanoma. There is no definitive data on what the preferred therapy is in the case of inoperable or metastatic relapse after previous adjuvant therapy [11]. It is important to mention, that BRAF + MEK inhibitors are a valuable option in adjuvant therapy in stage-III melanoma [12]. BRAF + MEK inhibitors give fast responses in *BRAF*-mutated advanced melanomas and disease control with a limited duration of responses, which is related to the activation of resistance mechanisms. Due to these characteristics therapy should be considered as a treatment of choice in patients with symptomatic disease and/or high tumor mass, but, in the majority of cases, the treatment of choice is immunotherapy (preferably a combination of anti-PD-1 and anti-CTLA-4) [13, 14].

Conflict of interest

P. Rutkowski has received honoraria for lectures and Advisory Boards from Novartis, MSD, BMS, Roche, Pierre Fabre, Pfizer, Sanofi, Merck, Blueprint Medicines, Philogen.

References

1. Rutkowski P, Mandala M. (ed.). New Therapies in Advanced Cutaneous Malignancies. Springer Nature 2021.
2. Rutkowski P, Wysocki PJ, Kozak K, et al. xpert recommendations on diagnostic-therapeutic management of melanoma patients. Oncol Clin Pract. , doi: 10.5603/2021.0042.
3. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. Clin Cancer Res. 2013; 19(5): 1225–1231, doi: 10.1158/1078-0432.CCR-12-1630, indexed in Pubmed: 23307859.
4. Ascierto PA, Dréno B, Larkin J, et al. 5-Year Outcomes with Cobimetinib plus Vemurafenib in Mutation-Positive Advanced Melanoma: Extended Follow-up of the coBRIM Study. Clin Cancer Res. 2021 [Epub ahead of print], doi: 10.1158/1078-0432.CCR-21-0809, indexed in Pubmed: 34158360.
5. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N Engl J Med. 2019; 381(7): 626–636, doi: 10.1056/NEJMoa1904059, indexed in Pubmed: 31166680.
6. Ascierto PA, Dummer R, Gogas HJ, et al. Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma. Eur J Cancer. 2020; 126: 33–44, doi: 10.1016/j.ejca.2019.11.016, indexed in Pubmed: 31901705.
7. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAFV600-mutant melanoma: an open-label, single arm, dual-centre, phase 2 clinical trial. Lancet Oncol. 2017; 18(4): 464–472, doi: 10.1016/s1470-2045(17)30171-7.
8. Valpione S, Carlino M, Mangana J, et al. Re-challenge with BRAF-directed treatment: A multi-institutional retrospective study. J Clin Oncol. 2017; 35(15_suppl): 9512–9512, doi: 10.1200/jco.2017.35.15_suppl.9512.
9. Cybulska-Stopa B, Rogala P, Czarnecka AM, et al. BRAF and MEK inhibitors rechallenge as effective treatment for patients with metastatic melanoma. Melanoma Res. 2020; 30(5): 465–471, doi: 10.1097/CMR.0000000000000662, indexed in Pubmed: 32221131.
10. Czarnecka AM, Teterycz P, Mariuk-Jarema A, et al. Treatment Sequencing and Clinical Outcomes in BRAF-Positive and BRAF-Negative Unresectable and Metastatic Melanoma Patients Treated with New Systemic Therapies in Routine Practice. Target Oncol. 2019; 14(6): 729–742, doi: 10.1007/s11523-019-00688-8, indexed in Pubmed: 31754963.
11. Keilholz U, Ascierto PA, Dummer R, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Ann Oncol. 2020; 31(11): 1435–1448, doi: 10.1016/j.annonc.2020.07.004, indexed in Pubmed: 32763453.
12. Hauschild A, Dummer R, Schadendorf D, et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected V600-Mutant Stage III Melanoma. J Clin Oncol. 2018; 36(35): 3441–3449, doi: 10.1200/JCO.18.01219, indexed in Pubmed: 30343620.
13. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019; 381(16): 1535–1546, doi: 10.1056/NEJMoa1910836, indexed in Pubmed: 31562797.
14. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022; 40(2): 127–137, doi: 10.1200/JCO.21.02229, indexed in Pubmed: 34818112.