OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2019, Vol. 15, Number 3

ISSN 2450–1654

VIA MEDICA

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology

https://journals.viamedica.pl/oncology_in_clinical_practice

Opinions presented in the articles do not necessarily represent the opinions of the Editors

Oncology in Clinical Practice (ISSN 2450–1654) 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, wap.viamedica.pl

18-0237.015.001

Editorial Address

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

Indexed in Index Copernicus (ICV 2018 = 84.45), Ulrich's Periodicals Directory and CAS.

According to the statement of the Polish Ministry of Science and Higher Education publication in the journal has been awarded with 20 points.

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

The journal "Oncology in Clinical Practice" is financed under Contract No. 790/P-DUNdem/2019 by the funds of the Minister of Science and Higher Education for the science promotion activities.

Ministerstwo Nauki i Szkolnictwa Wyższego

ONCOLOGY
IN CLINICAL PRACTICE
Official Journal of the Polish Society of Clinical Oncology
https://journals.viamedica.pl/oncology_in_clinical_practice 2019, Vol. 15, Number 3

VIA MEDICA

ORIGINAL ARTICLE

Monika Słowińska[1], Aldona Maciąg[1], Monika Dudzisz-Śledź[2], Izabela Łasińska[3], Tomasz Świtaj[2], Hanna Koseła-Paterczyk[2], Aleksandra Bolewska[1], Katarzyna Wróbel[1], Paweł Golusiński[4, 5, 6], Jacek Mackiewicz[3, 7, 8], Piotr Rutkowski[2], Witold Owczarek[1]

[1]Dermatology Clinic, Military Institute of Medicine, Central Clinical Hospital of the Ministry of National Defence in Warsaw, Poland
[2]Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Sklodowska-Curie Institute — Oncology Center in Warsaw, Poland
[3]Department of Clinical and Experimental Oncology, Heliodor Swiecicki Clinical Hospital, Medical University in Poznan, Poland
[4]Department of Head and Neck Cancer Biology, Faculty of Biology and Environmental Protection, Medical University in Poznan, Poland
[5]Department of Otolaryngology and Maxillofacial Surgery, University of Zielona Gora, Poland
[6]Head and Neck Surgery Ward and Laryngological Oncology Clinic, Greater Poland Cancer Center, Poznan, Poland
[7]Faculty of Biology and Environmental Protection, Medical University in Poznan, Poland
[8]Cancer Diagnosis and Immunology Unit, Greater Poland Cancer Center, Poznan, Poland

Vismodegib in the treatment of basal cell carcinoma — Polish clinical experience in the frame of therapeutic program

Address for correspondence:
Dr n. med. Monika Słowińska
Klinika Dermatologiczna
Wojskowy Instytut Medyczny
Centralny Szpital Kliniczny Ministerstwa
Obrony Narodowej w Warszawie
e-mail: monika.slowinska@yahoo.com

Oncology in Clinical Practice
2019, Vol. 15, No. 3, 139–149
DOI: 10.5603/OCP.2018.0041
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Introduction. Vismodegib is a small-molecule inhibitor of the sonic hedgehog pathway, registered for the treatment of patients with metastatic or locally advanced basal cell carcinoma, who were disqualified from surgical excision or radiotherapy. The full treatment refund from the National Health Fund has been available in Poland since 1st January 2018. The aim of the study was to analyse the frequency of occurrence of adverse events based on CTCAE and the treatment results based on the RECIST 1.1 criteria, in a group of patients treated for six or 12 months with vismodegib.

Material and methods. The patient database was gathered from three sites and consisted of 42 patients, who represented 53.8% of the patients treated with vismodegib in Poland. The duration of the treatment ranged between three weeks and 68 months. The median of the treatment period was 8.25 months (0.75–68); the median of the observation of patients treated for less than 12 months was eight months (6–11), and for those treated for more than 12 months it was 14 months (12–68).

Results. The summary of the treatment results after six and 12 months was performed on 29/42 and 17/42 patients accordingly. Complete response was achieved in 3/29 (10.3%) and 3/16 (17.6%) patients after six and 12 months of treatment, respectively, partial response in 13/29 (44.8%) and 5/16 (29.4%) patients, respectively, and stable disease in 13/29 (44.8%) and 8/16 (50.0%) patients, respectively. Progression of the disease was experienced by 7/42 (16.6%) patients within the period of 3–28 months of treatment. One patient with brain metastases died due to the progression of the disease. Adverse events were reported in 31/42 (73.8%) patients, more than one adverse event in a single patient was reported in 22/42 (52.3%) patients. No serious adverse events were observed.

Key words: vismodegib, basal cell carcinoma, treatment response rate, adverse events

Oncol Clin Pract 2019; 15, 3: 139–149

Introduction

Based on data from the National Cancer Registry, the incidence of skin cancer in the Polish population in 2010 was 6.8% in men and 7.5% in women [1]. The standardised rate for individuals aged 65 years or older was 146.4 and 96.8 in men and women, respectively. The number of registered skin cancers in 2010 was over 10,000. The exact skin cancer incidence in Poland is not known due to insufficient reporting to the National

Cancer Registry. A good reference for the European population may be a Danish study, which revealed basal cell carcinoma (BCC) incidence in 2005 accounting for 6074 cases/100,000 among women aged 65 years or older and 6347 cases/100,000 among men, with a 5–6-fold increase in morbidity between 1973 and 2008. The authors of the study predict, based on current statistical data, that by 2020 the incidence in the group over 65 years old will be 16,282/100,000 and 20,019/100,000 in women in men, respectively [2].

Basal cell carcinoma is slow growing, slightly and locally aggressive tumour. The metastatic rate is estimated to be around 0.0028–0.55% [3]. It occurs most frequently in patients over 65 years of age (constituting over 95% of cases) and is located mainly in the facial area, 30% of which are within the nose, 7% around the orbit, and about 6% of lesions concern the ear. The occurrence of one BCC is associated with a 40% risk of occurrence a second one in the next five years; if there was more than one BCC, the risk of the next lesion increases to 75% [2, 3].

Vismodegib is a small-molecule drug belonging to the group of hedgehog pathway (Hh) inhibitors, which has been registered by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), based on results of the ERIVANCE and STEVIE studies for the treatment of patients with symptomatic metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC), who are ineligible for surgery or radiotherapy [4–6]. Since 1st January 2017, vismodegib has been accessible to patients in Poland as part of a drug program reimbursed by the National Health Fund (NFZ). The final qualification of patients for the program is carried out by the Coordination Team for the Treatment of Basal Cell Skin Cancer, appointed by the President of the NFZ. During the period from 1st August 2017 to 30th September 2018 a total of 78 patients started treatment with vismodegib in Poland.

Aim of work

The aim of the study was to analyse groups of patients qualified for vismodegib therapy, to assess the frequency of adverse events with determination of their severity according to Common Terminology Criteria for Adverse Events (CTCAE), and to summarise the outcomes after six and 12 months. Data regarding patients came from three centres: the Dermatology Clinic, Military Institute of Medicine, Central Clinical Hospital of the Ministry of National Defence in Warsaw, the Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Sklodowska-Curie Institute — Oncology Center in Warsaw, and the Department of Clinical and Experimental Oncology, Heliodor Swiecicki Clinical Hospital, Medical University in Poznan. These centres had a total of 42 (53.8%) of the 78 patients treated with vismodegib throughout Poland.

Patients and methods

The analysis included 42 patients (30 male and 12 female) aged 33–87 years (mean 63.2). All patients were qualified to the program, according to inclusion criteria, due to the presence of histopathologically confirmed, locally advanced basal cell carcinoma; in seven out of 42 patients the additional criterion for inclusion was coexisting metastases (CNS 1/9, liver 1/9, lung 5/9, lymph nodes 1/9, and bones 1/9). In addition, 5/42 patients were diagnosed with Gorlin-Goltz syndrome (GGS). At qualification for participation in the program, all patients were disqualified from possible further surgical treatment and radiotherapy. Of the 42 patients, 27 had previously been treated surgically, 16 had had radiotherapy, and four had received chemotherapy; 2/42 patients had been unsuccessfully treated with three and 13/42 patients with two of the above methods. All patients met the remaining criteria for participation in the program, i.e. regarding laboratory tests, imaging evaluation, and performance status (PS) based on the Eastern Cooperative Oncology Group (ECOG), in accordance with the NFZ guidelines [7, 8]. The drug in the form of capsules was taken orally in a single daily dose of 150 mg. Treatment was continued until the exclusion criteria were met: documented progression during the use of the drug, the occurrence of hypersensitivity symptoms to vismodegib or any of the excipients, the occurrence of an adverse event preventing further treatment, or patient withdrawal. The contraindication to vismodegib treatment included pregnancy and breastfeeding. Due to the teratogenicity of the drug it was necessary to use effective contraception during the therapy and after its completion (women for two years and men for two months). The duration of treatment in the 42 patients ranged between three weeks and 68 months. The analysis of the occurrence of individual adverse reactions and their severity according to CTCAE version 5.0 included 42 patients [9]. The patients were carefully monitored every 2–3 months based on medical history, physical examination, laboratory tests, photographic documentation, and imaging examinations [8]. Response to treatment was assessed according to RECIST 1.1 after six and 12 months in 29/42 and 17/42 patients, respectively [10]. The reason for treatment discontinuation and the time to progression in patients who did not respond to treatment were also shown. A summary of all data collected in the analysed population is presented in Table 1.

Table 1. Summary of data of 42 patients treated with vismodegib (COI — Cancer Centre and Institute of Oncology; WIM — Military Institute of Medicine, SKUMP — Clinical Hospital, Medical University in Poznan)

Patient number/ /Centre name	Sex: F — female, M — male	Age	Diagnosis: metastatic BCC — 1, locally advanced BCC — 2	Meta-stases localisation	Previous treatment (Surgery — S, Radiotherapy — R, Chemotherapy — ChT)	Response after 6 months of treatment according to RECIST 1.1. (CR, PR, SD, PD)	Response after 12 months of treatment according to RECIST 1.1.	Total duration of therapy/ /months	Adverse events (AE) according to CTCAE version 5.0	Reason for treatment discontinuation: due to AE — 1, due to PD — 2, other — 3	Death Yes (Y)/ /No (N)
1 SKUMO	M	68	2		S	CR	CR	60	Hair loss G1		
2 SKUMO	M	75	2		S, R	PR	0	8	Loss of appetite G2		
3 SKUMO	M	76	2		0	PR	0	8	Muscle weakness G1, loss of appetite G2		
4 SKUMO	M	56	2		S, R	PR	0	7	0		
5 SKUMO	M	86	2		S, R (brachytherapy)		0	4	0		
6 SKUMO	M	61	2		S		0	2	0		
7 SKUMO	M	68	2		0		0	2	0		
1 COI	F	76	2		0			3.5	0		
2 COI	M	62	2		R			2.5			
3 COI	F	72	2		S, ChT	PR	PR	12	0		
4 COI	M	68	2		S	SD	SD	12	Asthenia G1, loss of appetite G2		
5 COI	F	85	2		S			0.75	0		
6 COI	F	82	2		R	SD	SD	14	Muscle cramps G1		
7 COI	M	53	2		S	SD	SD	14	Muscle cramps G1, loss of appetite G1, dysgeusia G1, hair loss G1		
8 COI	F	61	2		0	SD		8	Muscle cramps G1, loss of appetite G1, headache G1, dry skin of the face G1		
9 COI	F	86	2		0			3	Muscle cramps G1, loss of appetite G1		
10 COI	F	64	2			PR	PR	12	Muscle cramps G1		

→

Table 1 (cont.). Summary of data of 42 patients treated with vismodegib (COI — Cancer Centre and Institute of Oncology; WIM — Military Institute of Medicine, SKUMP — Clinical Hospital, Medical University in Poznan)

Patient number/ /Centre name	Sex: F — female, M — male	Age	Diagnosis: metastatic BCC — 1, locally advanced BCC — 2	Meta-stases localisation	Previous treatment (Surgery — S, Radiotherapy — R, Chemotherapy — ChT)	Response after 6 months of treatment according to RECIST 1.1. (CR, PR, SD, PD)	Response after 12 months of treatment according to RECIST 1.1.	Total duration of therapy/ /months	Adverse events (AE) according to CTCAE version 5.0	Reason for treatment discontinuation: due to AE — 1, due to PD — 2, other — 3	Death Yes (Y)/ /No (N)
11 COI	M	75	2,1	Lung	R	SD		6	Pulmonary embolism G3		
12 COI	M	61	2,1	Bones	S, R			5	Anaemia G3		
13 COI	F	66	2		0	PR	PR	20	Increased CPK level G1		
14 COI	M	70	2		S, R, ChT	PR	SD	20	Loss of appetite G1, body weight loss G1		
15 COI	M	61	2,1	Lung	S, R	SD		8.5	Increased CPK level G1		
16 COI	M	63	2		S	SD		10	Increased CPK level G1		
17 COI	F	71	2	0	S, R			3	Loss of appetite G1, painful muscle cramps G1		
18 COI	M	35	2.1	Lung	S, R, ChT	SD	SD	28	Lack of data	2	N
19 COI	M	85	2	0	S	SD	SD	21	Loss of appetite G1, arthralgia G2, myalgia G2, asthenia (fatigue) G2, abdominal pain G2, body weight loss G2, muscle cramps G1		
20 COI	F	81	2.1	Lung		SD		7	Hair loss G1, muscle cramps G1, loss of appetite G1, dysgeusia G1	2	N
21 COI	M	87	2	Liver	S			3	Loss of appetite G1, general asthenia G1	2	N
1 WIM	M	63	2	0	S	SD	SD	14	Dysgeusia G1, muscle cramps G2, hair loss G2		

→

Table 1 (cont.). Summary of data of 42 patients treated with vismodegib (COI — Cancer Centre and Institute of Oncology; WIM — Military Institute of Medicine, SKUMP — Clinical Hospital, Medical University in Poznan)

Patient number/ /Centre name	Sex: F — female, M — male	Age	Diagnosis: metastatic BCC — 1, locally advanced BCC — 2	Meta-stases localisation	Previous treatment (Surgery — S, Radiotherapy — R, Chemotherapy — ChT)	Response after 6 months of treatment according to RECIST 1.1. (CR, PR, SD, PD)	Response after 12 months of treatment according to RECIST 1.1.	Total duration of therapy/ /months	Adverse events (AE) according to CTCAE version 5.0	Reason for treatment discontinuation: due to AE — 1, due to PD — 2, other — 3	Death Yes (Y)/ /No (N)
2 WIM	M	60	2,1	Lung, mediastinal lymph nodes	S, ChT	PR	PD	13	Dysgeusia G1, muscle cramps G1, hair loss G1	2	N
3 WIM	M	69	2	0	S, R	SD	SD	16	Muscle cramps G2, loss of appetite G2, asthenia (fatigue) G2, nausea G2, loss of appetite G2, body weight loss G1	2	N
4 WIM	M	57	2	0	S, R	CR	CR	14	Muscle cramps G1, hair loss G2		
5 WIM	M	39	2	0	S	PR	PR	12	Muscle cramps G1, hair loss G2		
6 WIM	F	48	2	0	S, R	CR	CR	68	Muscle cramps G1, hair loss G2		
7 WIM	M	33	2	0	S	PR	PR	13	Muscle cramps G1, nausea G1, hair loss G2, body weight loss G1		
8 WIM	M	55	2.1	CNS	S, R	SD	PD	12	0	3	Y
9 WIM	M	59	2	Bones	0	PR		11	Dysgeusia G1, muscle cramps G1, hair loss G1	2	N
10 WIM	M	75	2	0	S, R	PR		6.5	Dysgeusia G1, muscle cramps G1, hair loss G1		
11 WIM	M	67	2	0	0	PR		6	Dysgeusia G1, muscle cramps G1, hair loss G1		
12 WIM	M	48	2	0	S			3	Dysgeusia and olfactory disorders G1, muscle cramps G1, asthenia G1, increased number of bowel movements G1		

→

Table 1 (cont.). Summary of data of 42 patients treated with vismodegib (COI — Cancer Centre and Institute of Oncology; WIM — Military Institute of Medicine, SKUMP — Clinical Hospital, Medical University in Poznan)

Patient number/ /Centre name	Sex: F — female, M — male	Age	Diagnosis: metastatic BCC — 1, locally advanced BCC — 2	Meta-stases localisation	Previous treatment (Surgery — S, Radiotherapy — R, Chemotherapy — ChT)	Response after 6 months of treatment according to RECIST 1.1. (CR, PR, SD, PD)	Response after 12 months of treatment according according to RECIST 1.1.	Total duration of therapy/ /months	Adverse events (AE) according to CTCAE version 5.0	Reason for treatment discontinuation: due to AE — 1, due to PD — 2, other — 3	Death Yes (Y)/ /No (N)
13 WIM	M	83	2	0	0			3	Muscle cramps G1, dysgeusia G1		
14 WIM	F	80	2	0	0			1	0		

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease; AE — adverse event

Results

The outcome summary of 42 patients is presented in Table 2 and 3. At the time of writing, only 29 patients have completed 6 months of therapy, and 17 of them have completed 12 months. In the latter group there were three patients with metastases. The duration of treatment differed significantly and was between 0.75 and 68 months, with the median duration of treatment 8.25 months. Among patients who were treated for less than 12 months the median follow-up was 8 months, while in patients treated for more than 12 months the median follow-up was 14 months.

Table 4 presents the results of treatment effectiveness after 6 and 12 months in the study group in comparison with the results of the ERIVANCE and STEVIE studies as well as the EAS (expanded access study). However, the significant differences in the sizes of individual groups of patients, as well as the percentage of mBCC in the study group and the duration of treatment, should be highlighted [4, 5, 11].

Table 5 presents a summary of occurrence of adverse reactions among 42 patients, as compared to the ERIVANCE, STEVIE, and EAS studies. It should be added that whilst 7 out of 42 patients discontinued treatment due to disease progression, there was no case of discontinuation of treatment due to adverse events, which occurred in a total of 73.8% of patients; however, 74.3% of AEs had G1 and 23% had G2 intensity according to CTCAE version 5.0. It should also be concluded that the frequency of reported adverse reactions both in total and in relation to individual signs/symptoms was significantly lower than demonstrated in the ERIVANCE, STEVIE, and EAS studies [4, 5, 11].

Discussion

The efficacy and safety of vismodegib treatment have been confirmed in the multicentre, non-randomised, international ERIVANCE study, the results of which were published in 2012 [4]. The study group included 104 patients with locally advanced (laBCC; 71/104, in total 63 patients were included in the final analysis) and metastatic basal cell carcinoma (mBCC; 33/104). The duration of treatment was 0.7–18.7 months, and the median was 10 months. The objective response rate (ORR) in the first group was 43% (95% CI, 31–56, $p < 0.001$) and 30% in the second group (95% CI; 16–48; $p = 0.001$), while the response rate (RR) was 21%. Disease stabilisation (SD) was obtained in 64% and 38% of patients, respectively, while progression of disease (PD) was found in 3% and 13% of patients, respectively. Median duration of response (DOR) in both groups was 7.6 months, and the median

Table 2. A summary of treatment responses according to the RECIST 1.1 criteria after 6 and 12 months of therapy

Treatment responses according to the RECIST 1.1 criteria	After 6 months of therapy (n = 29)	After 12 months of therapy (n = 17)
CR	3 (10.3%)	3 (17.6%)
PR	13 (44.8%)	5 (29.4%)
ORR (CR + PR)	16 (55.1%)	8 (47%)
SD	13 (44.8%)	8 (50.0%)
PD	Achieved by 7 out of 42 patients (16.6%): — 1 after 3 months — 0 after 6 months — 1 after 7 months — 1 after 11 months — 1 after 12 months — 1 after 13 months — 1 after 16 months — 1 after 28 months	

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease

Table 3. A summary of treatment responses according to the RECIST 1.1 criteria after 6 and 12 months of therapy in patients with metastatic cancer (7/42; of whom 3 patients were treated for less than 12 months, 1 patient was treated 3 months and therefore was not included in the summary)

Treatment responses according to the RECIST 1.1 criteria	After 6 months of therapy (n = 6)	After 12 months of therapy (n = 3)
CR	0	0
PR	1	0
SD	5	1
PD		2

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease

progression-free survival (PFS) was 9.5 months. The results of this study led to the approval of vismodegib by the FDA and EMA for the treatment of advanced BCC patients.

In 2015 Lacouture et al. published the preliminary results of a prospective multicentre observational study planned for eight years to assess efficacy and safety in about 750 patients with advanced BCC stratified to three treatment groups: C1 — patients previously not treated with vismodegib, who will receive vismodegib, C2 — patients previously treated with vismodegib, who will undergo surgical treatment, and C3 — patients with Gorlin-Goltz syndrome with advanced BCC or numerous non-advanced BCC lesions, who may have been previously treated with sonic hedgehog pathway inhibitors [12]. The study started in June 2012 but was terminated by the sponsor in April 2017 due to the high percentage of patients who discontinued treatment (but not due to safety aspects). The authors summarised the treatment in the C1 group containing 77 patients and C2 containing 144 patients; ORR (95% CI) in C1 group was 68% (56–78), CR 45% (35/77), PR 22% (17/77), while in the C2 group it was 61%, 60% (86/144), and 1% (2/144), respectively. There were adverse reaction events in 82% (63/77) of patients in the C1 group and in 15% (22/144) in the C2 group, and serious adverse events in 14% (11/77) and 8% of patients (11/144), respectively. Interestingly, SCC (squamous cell carcinoma) was found only in the C2 group (64% of patients; 7/11).

In 2014, based on results of the expanded access study (EAS), Chang et al. evaluated the effectiveness of treatment of 95 patients (58.9% — laBCC, 41% — mBCC), after duration of treatment 5.5 months (0.4–19.6), including four patients previously treated with vismodegib [11]. In Table 4 it can be observed that the group of patients with laBCC in the EAS study achieved results similar to those presented by the Polish group after six months of treatment. This consistence can be interpreted in light of the small

Table 4. A comparison of treatment effectiveness of locally advanced basal cell carcinoma (laBCC) and metastatic basal cell carcinoma (mBCC) in the study group with the ERIVANCE, STEVIE, and EAS studies [4, 5, 11]

Treatment responses according to the RECIST 1.1 criteria	After 6 months of therapy (n = 29/42)	After 12 months of therapy (n = 17/42)	The results of the STEVIE study; median treatment duration: 9 months (laBCC) and 13 months (MBCC) (n = 482/499)	The results of the expanded access study (EAS); median treatment duration 5.5 months (n = 95/119)	The results of the ERIVANCE study; median treatment duration 10 months (n = 96/104)
Patient groups	laBCC 79.3%; mBCC 20.6%	laBCC 82.3%; mBCC 17.6%	laBCC 93.9%; mBCC 6%	laBCC 58.9%; mBCC 41.0%	laBCC 52%; mBCC 31.7%
Gorlin-Goltz syndrome	17.2% 5 — laBCC 0 — mBCC	23.5% 4 — laBCC 0 — mBCC	20% (98/485) 96 — laBCC 2 — mBCC	15.9% (19/119) 12 — laBCC 7 — mBCC	31% (22/104) 22 — laBCC 0 — mBCC
CR	10.3% 3 — laBCC 0 — mBCC	17.6% 3 — laBCC 0 — mBCC	32% 34% laBCC 7% mBCC	10.7% laBCC 5.1% mBCC	31.7% laBCC O% mBCC
PR	44.8% 12 — laBCC 1 — mBCC	29.4% 5 — laBCC 0 — mBCC	33% 33% laBCC 31% mBCC	35.7% laBCC 25.6% mBCC	28.5% laBCC 45.4% mBCC
ORR /OR (CR + PR)	55.1% 15 — laBCC 1 — mBCC	47% 8 — laBCC 0 — mBCC	66.7% laBCC 37.9% mBCC	46.4% laBCC 30.8% mBCC	60.3% laBCC 45.5% mBCC
SD	44.8% 8 — laBCC 5 — mBCC	50.0% 7 — laBCC 1 — mBCC	27% 26% laBCC 34% mBCC	48.2% laBCC 51.3% mBCC	38% laBCC 64% mBCC
PD	3.4% 0 — laBCC 1 — mBCC (after 3 months)	17.6% 0 — laBCC 3 — mBCC	3% 2% laBCC 14% mBCC	0% laBCC 7.7% mBCC	9.5% laBCC 6% mBCC

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease; laBCC — locally advanced basal cell carcinoma; mBCC — metastatic basal cell carcinoma

number of patients who were treated for 12 months, so the majority of data from authors of this article relate to a group with a duration of treatment similar to the EAS.

The STEVIE study, the first results of which were published in 2015, involved 1277 patients treated with vismodegib, of whom 499 (468 with laBCC and 31 with mBCC) were evaluated in safety set and 482 (453 with laBCC and 29 with mBCC) in an efficacy set [5]. The median duration of treatment was 36.3 weeks (17.6–60.0) for laBCC and 52 weeks (23.3–76.0) for mBCC patients. Based on the investigators assessment, overall response (OR) was found in 302 (66.7%, 62.1–71.0) of 453 laBCC patients, including 153 complete responses (CR) and 149 partial responses (PR). In total 11 (37.9%, 20.7–57.7) out of 29 mBCC patients responded to the treatment (OR), with two (7%) and nine (31%) patients receiving complete and partial response, respectively. In total 400 (80%) patients discontinued the study: 36% due to adverse reactions, 14% due to disease progression, and 10% based on the patient's decision. The safety profile was comparable to that in the ERIVANCE study. Of note, there were far fewer adverse reactions reported among patients in the Polish group compared to 98–100% of patients from the studies cited above (Table 5), and none of the patients discontinued the treatment due to AEs occurrence. Based on the data from the STEVIE and ERIVANCE studies, it is known that the average time to onset of adverse reactions varies depending on its nature (2.8 months for muscle cramps, 5.5 months for alopecia, and 6.5 months for dysgeusia) and account for two months on average [4, 5]. Hence, the short duration of treatment and the small number of Polish patients could be an explanation for these discrepancies. The concentration of these patients in three centres with extensive experience in the treatment of skin cancers is important for the reported results of the group of patients examined by the authors of this article.

In 2016 Chang et al. evaluated the effectiveness of treatment of patients with Gorlin-Goltz syndrome, qualified as laBCC or mBCC in the ERIVANCE and

Table 5. A collation of adverse events (AE) incidence in the study group in comparison to the ERIVANCE, STEVIE, and EAS studies [4, 5, 11]

	Total number of AEs	Intensity grade according to CTCAE, version 5.0	AE incidence in the ERIVANCE study	AE incidence in the STEVIE study	AE incidence in EAS study
Total AE	AE — 73.8% (31/42) > 1 AE/patient 52.3% (22/42)	G1 —74.3% (58/78) G2 —23.0% (18/78) G3 — 2.5% (2/78)	100% (104/104) > 1–2 AE/ /patient 57%	98% (491/499)	97.5% (116/119) G1–2 = 67.2% (80/119) G3 = 20.1% (24/119) G4 = 7.5% (9/119) G5 = 2.5% (3/119)*
Muscle cramps	47.6% (20/42)	G1 — 18 G2 — 2	68%	64%	70.6%
Hair loss	28.5% (12/42)	G1 — 7 G2 — 5	63%	62%	58%
Loss of appetite	28.5% (12/42)	G1 — 8 G2 — 4	23%	25%	
Dysgeusia	23.8% (10/42)	G1 — 9 G2— 1	51%	54%	70.6%
Asthenia/fatigue	11.9% (5/42)	G1 — 3 G2 — 2	36%	28%/16%	19.3%
Body weight loss	9.5% (4/42)	G1 — 3 G2 — 1	46%	33%	16%
Increased creatine kinase level	7.1% (3/42)	G1 — 3	0	0	
Nausea	4.7% (2/42)	G1 — 1 G2 — 1	29%	16%	19.3%
Abdominal pain	2.3% (1/42)	G2 — 1			
Headache	2.3% (1/42)	G1 — 1			
Olfactory disorders	2.3% (1/42)	G1 — 1			
Anaemia	2.3% (1/42)	G3 — 1			
Pulmonary embolism	2.3% (1/42)	G3 — 1			
Myalgia	2.3% (1/42)	G1 — 1			
Increased number of bowel movements	2.3% (1/42)	G1 — 1	Diarrhoea 22%	Diarrhoea 17%	Diarrhoea 25.2%
Dry skin	2.3% (1/42)	G1 — 1			
Arthralgia	2.3% (1/42)	G2 — 1			
Muscle weakness	2.3% (1/42)	G1 — 1			
Death due to progression disease	2.3% (1/42)			6% 31/499 patients died due to: — progression of disease 5/499 — AE 21/499 — others 5/499	2.5% died 2 with mBCC due to progression of disease; 1 with laBCC due to SCC dissemination
SAE			25%	22% (108/499) deterioration of general health, dehydration, SCC, pneumonia	SAE G3–G5 15.1% (18/119): *mesothelioma*, recurrence of B-cell lymphoma, recurrence/ /dissemination of SCC, muscle cramps

SAE — serious adverse event; AE — adverse event; CTCAE — Common Terminology Criteria for Adverse Events; SCC — squamous cell carcinoma; laBCC — locally advanced basal cell carcinoma; mBCC — metastatic basal cell carcinoma

EAS studies [13]. In the ERIVANCE study all patients diagnosed with GGS were in the laBCC group (21/63), while in the EAS study 12/56 study in the laBCC group and 6/39 in the mBCC group. Although the authors did not find a statistically significant difference in treatment efficacy between GGS and non-GGS patients, there is a tendency towards a lower percentage of SD and PD in the GGS group. In the ERIVANCE study ORR (CR and PR) in patients with GGS was 81% (CR — 38%, OR — 43%), SD — 14%, and PD — 5%, whereas in the group without GGS, 50% (CR — 29%, PR — 21%), 29%, and 12%, respectively. In turn, in the EAS study the above differences disappear: in the laBCC group with GGS the ORR was 33% (CR — 8%, PR — 25%), SD — 50%, and PD — 17%, while without GGS the ORR was 50% (CR — 11%, PR — 39%), SD — 48%, and PD — 0%. In the group of patients with mBCC and GGS the ORR was 50 (CR — 33%, PR — 17%), SD — 50%, and PD — 0%, while in the group without GSS the ORR was 27% (CR — 0%, PR — 27%), SD — 52%, and PD — 9%. In the Polish group 5/42 patients were diagnosed with GGS. Among patients treated for six months, they constituted 17.2% (5), of whom four (23.5%) were treated for 12 months. All patients achieved a response (CR or PR).

In a publication from 2017 summarising the OS after a period of approximately 39.1 months of follow-up of 104 patients from the ERIVANCE study, Sekulic et al. reported 30 deaths (51.5%, 17/33 in mBCC patients and 20.6%, 13/63 in laBCC patients); the median OS for mBCC was 33.4 months, whereas for laBCC it was not achieved because it exceeded the survival rate for this group of patients [14]. The median follow-up for OS assessment in both groups was 39.1 months, and the estimated survival according to Kaplan-Meier after the first year was 78.7% in the mBCC group (95% CI, 64.7–92.7) and 93.2% (95% CI, 86.8–99.6) in the laBCC group. The two-year survival rates of these patients were 62.3% (95% CI, 45.4–79.3) in the mBCC group and 85.5% (95% CI, 76.1–94.8) in the laBCC group. The observations of the authors of this article do not allow for the assessment of data after such a long period of observation. The problem that should be taken into account in the treatment of patients with advanced BCC is the emerging of resistance to vismodegib, resulting from the mutation of the Hh pathway proteins and the genes that they regulate, as well as from the transformation/coexistence of the squamous cell carcinoma component within BCC [15]. The situation is hampered by the fact that in Poland there are no other therapeutic options available for these patients. The authors of this article await the upcoming results of efficacy and safety of vismodegib in combination with radiotherapy or surgical treatment in adjuvant and neoadjuvant therapy [16, 17].

Conclusions

Currently, vismodegib is the only therapeutic option available in Poland for patients with locally advanced or metastatic basal cell carcinoma, who cannot be treated with surgery or radiotherapy [18]. Despite common side effects, the majority of them had G1 or G2 intensity according to CTCAE, and the results presented confirm the efficacy of vismodegib in routine oncological practice as part of the NFZ drug program.

References

1. Krajowy Rejestr Nowotworów - http://onkologia. org pl/nowotwory--skory-c44.
2. Flohil SC, de Vries E, Neumann HA, et al. Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol. 2011; 91(1): 24–30, doi: 10.2340/00015555-1009, indexed in Pubmed: 21264452.
3. Bichakjian CK, Alam M, Kim JYS, et al. Work Group, Invited Reviewers. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol. 2018; 78(3): 540–559, doi: 10.1016/j.jaad.2017.10.006, indexed in Pubmed: 29331385.
4. Sekulic A, Migden MR, Oro AE, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma, N Engl J Med. 2012; 366: 2171–2179.
5. Basset-Seguin N, Hauschild A, Grob JJ, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. The Lancet Oncology. 2015; 16(6): 729–736, doi: 10.1016/s1470-2045(15)70198-1.
6. Wismodegib - Charakterystyka produktu leczniczego. https://www.roche.pl/content/dam/roche_poland_rwd/pl_PL/documents/SmPC/erivedge.pdf.
7. Eastern Cooperative Oncology Group (ECOG) http://www.npcrc.org/files/news/ECOG_performance_status.pdf.
8. Załącznik B.88. do programu leczenia zaawansowanego raka podstawnokomórkowego wismodegibem. http://onkologia-online pl/upload/obwieszczenie/2016 12 28/b/b. ; 88: pdf.
9. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017 U.S. Department Of Health And Human Services https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
10. Płużański A. Kryteria oceny odpowiedzi na leczenie RECIST 1.1. Nowotwory. Journal of Oncology. 2014; 64(4): 331–335, doi: 10.5603/njo.2014.0055.
11. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. J Am Acad Dermatol. 2014; 70(1): 60–69, doi: 10.1016/j.jaad.2013.09.012, indexed in Pubmed: 24189279.
12. Lacouture M, Guillen J, Kudchadkar R, et al. The RegiSONIC Disease Registry Study: Safety and effectiveness of vismodegib or surgery as primary treatment in patients with locally advanced basal cell carcinoma. European Journal of Cancer. 2015; 51: S679–S680, doi: 10.1016/s0959-8049(16)31859-7.
13. Chang AL, Arron ST, Migden MR, et al. Safety and efficacy of vismodegib in patients with basal cell carcinoma nevus syndrome: pooled analysis of two trials. Orphanet J Rare Dis. 2016; 11(1): 120, doi: 10.1186/s13023-016-0506-z, indexed in Pubmed: 27581207.
14. Sekulic A, Migden MR, Basset-Seguin N, et al. ERIVANCE BCC Investigators. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. BMC Cancer. 2017; 17(1): 332, doi: 10.1186/s12885-017-3286-5, indexed in Pubmed: 28511673.
15. Zhao J, Quan H, Xie C, et al. NL-103, a novel dual-targeted inhibitor of histone deacetylases and hedgehog pathway, effectively overco-

mes vismodegib resistance conferred by Smo mutations. Pharmacol Res Perspect. 2014; 2(3): e00043, doi: 10.1002/prp2.43, indexed in Pubmed: 25505589.
16. Kwon GP, Ally MS, Bailey-Healy I, et al. Update to an open-label clinical trial of vismodegib as neoadjuvant before surgery for high-risk basal cell carcinoma (BCC). J Am Acad Dermatol. 2016; 75(1): 213–215, doi: 10.1016/j.jaad.2016.02.1235, indexed in Pubmed: 27317518.
17. Gathings RM, Orscheln CS, Huang WW. Compassionate use of vismodegib and adjuvant radiotherapy in the treatment of multiple locally advanced and inoperable basal cell carcinomas and squamous cell carcinomas of the skin. J Am Acad Dermatol. 2014; 70(4): e88–e89, doi: 10.1016/j.jaad.2013.11.032, indexed in Pubmed: 24629372.
18. Rutkowski P, Owczarek W. (eds). Skin carcinomas. Oncol Clin Pract. 2018; 14(3): 129–147.

VIA MEDICA

REVIEW ARTICLE

Kinga Winiarczyk, Aleksandra Piórek, Maciej Krzakowski

Department of Lung and Thoracic Cancers, Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland

ALK, ROS1 and EGFR next-generation tyrosine kinase inhibitors in advanced non-small-cell lung cancer

Address for correspondence:
Lek. Kinga Winiarczyk
Klinika Nowotworów Płuca
i Klatki Piersiowej,
Centrum Onkologii
— Instytut im. M. Sklodowskiej-Curie
ul. Roentgena 5, 02–871 Warszawa
e-mail: kwiniarczyk@coi.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 3, 150–157
DOI: 10.5603/OCP.2018.0042
Translation: e-CORRECTOR

ISSN 2450–1654

ABSTRACT

Non-small-cell lung cancer (NSCLC) is the most common cancer in men and the second most common in females. In previous years the significance of some molecular disorders in pathogenesis NSCLC was proven and the value of targeted therapies in the treatment of patients was documented. In subjects with abnormalities of *EGFR*, *ALK* and *ROS1* genes, appropriate tyrosine kinase inhibitors (TKIs) may be used. The use of these drugs in the first and second treatment lines has affected a significant improvement in the prognosis in this subgroup of patients. The article presents mechanisms of action and data on the clinical value of lorlatinib, brigatinib and dacomitinib in the treatment of patients with advanced lung of lung cancer.

Key words: non-small-cell lung cancer, kinase inhibitors, lorlatinib, brigatinib, dacomitinib

Oncol Clin Pract 2019; 15, 3: 150–157

Introduction

Lung cancer is the most commonly diagnosed cancer in men and the second, after breast cancer, most common cancer in women. At the same time, it is the main cause of cancer deaths among both men and women (about 1.7 million per year) [1]. In about 80–85% of patients, non-small cell lung cancer (NSCLC) is diagnosed [2]. The generalised stage of the disease is initially found in more than 40% of patients [2]. Histological type and other pathomorphological factors are now routinely taken into account when choosing the type of treatment. In recent years, the importance of some molecular disorders in the pathogenesis of NSCLC has been demonstrated and the value of targeted therapies in the treatment of patients with this diagnosis has been shown. Currently, the standard is an individual approach in choosing the optimal procedure. In patients with abnormalities of epidermal growth factor receptor (*EGFR*) gene, anaplastic lymphoma kinase (*ALK*) gene, and *ROS1* gene it is possible to use appropriate tyrosine kinase inhibitors. The use of these drugs in the first and second line of treatment has resulted in significant improvement of prognosis in this subgroup of patients. The observed results of treatment confirmed the validity of searching for new, even more effective molecular target drugs, also effective in patients with developed resistance to earlier therapies or in the group of patients with metastases to the central nervous system (CNS). The article presents the current state of knowledge and potential uses of lorlatinib, brigatinib, and dacomitinib — next generation EGFR ALK/ROS1 tyrosine kinase inhibitor (TKI).

Lorlatinib

Pharmacological characteristics of lorlatinib

Lorlatinib (PF-06463922) is a third-generation low-molecular-weight inhibitor of ALK and ROS1 TKI. It is characterised by high affinity and strong inhibition of kinase. It also shows inhibitory action in the case

of G1202R mutation — the most common secondary mutation responsible for the development of resistance to ALK TKI of previous generations. Lorlatinib has a macrocyclic structure, which distinguishes it from other ALK inhibitors. Thanks to its structure, it has greater metabolic stability and the ability to pass through the blood-brain barrier. Lorlatinib is an orally bioavailable drug. After a single dose (10–200 mg), it is absorbed, reaching its maximum plasma concentration within 1–2 hours. The elimination phase half-life of lorlatinib ranges from 19.0 to 28.8 hours at doses of 10, 50, 75, 100, and 200 mg [3]. Results of *in vitro* and *in vivo* studies indicate that lorlatinib may change the pharmacokinetics of other drugs that are metabolised by P450 cytochrome isoenzymes and are administered at the same time. Therefore, according to the Phase II study, concomitant use of CYP3A inhibitors is not allowed for at least 12 days before the first dose of lorlatinib [3].

Clinical trials with lorlatinib

Phase I study

The phase I multi-centre study was designed to determine the pharmacokinetics and maximum tolerable dose, and to assess the adverse effects of lorlatinib in patients with advanced NSCLC with current *ALK* (77%) or *ROS1* (23%) gene rearrangement [4]. Other eligibility criteria included performance status according to the Eastern Cooperative Oncology Group (ECOG 0–1) and proper function of organs. In the 54 patients enrolled in the study, two or more TKI therapies were previously used in 28 patients and 39 (72%) had metastases to the CNS. Lorlatinib was administered orally at doses from 10 to 200 mg once daily or 35 to 100 mg twice daily. A well-tolerated dose — recommended for further studies — was set at 100 mg once daily. Among 41 *ALK*-positive patients the objective response rate (ORR) was found in 19 patients [46%; 95% confidence interval (CI) 31–63], including 11 out of 26 who previously used TKI (42%; 95% CI 23–63). In ROS1-positive patients, including seven patients previously treated with crizotinib, ORR was obtained in six patients (50%; 95% CI 21–79). Out of 24 patients with measurable target lesions in the CNS (46%; 95% CI 26–67) 11 had an intracranial objective response to the treatment.

Phase II study

In 2017, during the 18th World Conference on Lung Cancer, the results of the Phase II study were presented, in which 275 patients were included. The participants were divided into six cohorts depending on the previously applied therapy (Table 1) [5]. For five cohorts of 197 patients who previously received ALK inhibitors in different configurations, the percentage of ORR ranged from 33% (first line of treatment for ALK TKI other than crizotinib ± chemotherapy) to 74% (patients previously receiving only crizotinib). Objective intracranial responses in patients with CNS metastases ranged from 39% (three treatment lines ALK TKI ± chemotherapy) to 75% (crizotinib ± chemotherapy). The percentage of ORR was 90% in patients receiving lorlatinib as the first-line of treatment [5].

The American Food and Drug Administration (FDA) recognised lorlatinib as a breakthrough therapy in patients with advanced ALK-positive NSCLC [3, 6]. The definition of "breakthrough therapies" aims at accelerating the development and review of a potential new drug if it is intended to treat a serious or life-threatening disease, and initial clinical evidence suggests that the drug can be significantly effective compared to existing therapies [6].

Phase III study

A phase III study (CROWN) is currently underway, in which lorlatinib and crizotinib efficacy is compared in the first line of treatment of NSCLC with *ALK* rearrangement [7]. Patients are randomly assigned to arm A (lorlatinib 100 mg, 1 × daily) or arm B (crizotinib 250 mg, 2 × daily). The primary endpoint of the study is the evaluation of the influence of these therapies on the progression-free duration. Among the secondary endpoints, the percentage of objective intracranial responses in patients with measurable metastases to the CNS will also be assessed.

Table 1. Phase II study results with lorlatinib [5]

Earlier therapy	n	ORR — n (%)	N (metastases to CNS)	ORR (metastases to CNS) — n (%)
Without treatment	30	27 (90)	8	6 (75)
Crizotinib	27	20 (74)	17	10 (59)
Crizotinib + CHTH	32	21 (66)	20	15 (75)
Diffrent ALK TKI ± CHTH	27	9 (33)	12	5 (42)
2 lines ALK TKI ± CHTH	65	27 (42)	45	25 (56)
3 lines ALK TKI ± CHTH	46	16 (35)	38	15 (39)

CHTH — chemotherapy; ORR — objective response rate; ALK — anaplastic lymphoma kinase; TKI — tyrosine kinase inhibitor; CNS — central nervous system

Efficacy in patients with metastases to the central nervous system

Metastases to the brain are a common complication of cancer, and the effectiveness of drugs is significantly reduced in this area. Retrospective analysis showed that 20–30% of all NSCLC patients with *ALK* rearrangement had metastases in the CNS at the time of diagnosis (compared to 10–20% of patients with NSCLC regardless of *ALK* status) [8]. This number increases to 45–75% during the disease in patients using ALK inhibitors, which indicates that the disease in the CNS is a major problem in patients with *ALK* rearrangement. This is due to the presence of the blood-brain barrier. It is a semi-permeable barrier separating blood from extracellular CNS fluid. It consists of closely connected endothelial cells. It prevents the penetration of harmful substances into the brain, at the same time blocking the supply of many medicinal substances to it. The blood-brain barrier is not only a physical barrier to most substances, but thanks to P-glycoprotein and multidrug resistance proteins it also actively removes drugs [9]. The limitation for the first-generation ALK inhibitor crizotinib were frequent recurrences of the disease in the CNS. Next-generation inhibitors are characterised by better penetration to the CNS. Lorlatinib was designed to penetrate through the blood-brain barrier. This was confirmed by the pre-clinical studies of Collier et al. in which the penetration of lorlatinib was evaluated by positron emission tomography (PET) using carbon and fluorine marking [10]. In phase I clinical trials 46% of patients with measurable CNS metastases received an objective intracranial response to treatment [4]. The Phase II study showed high systemic and intracranial ORR (Table 1) in patients treated with the first line of treatment as well as in those receiving TKI ALK [5].

Efficacy in patients with drug resistance

Regardless of the type of TKI ALK used, disease progression occurs in patients treated with these drugs about 12 months after the onset of therapy [8]. However, the mechanisms of molecular progression vary. In about 50–60% of patients with acquired resistance to first-generation ALK TKI (crizotinib) activation of other cellular transmission pathways starting with EGFR or IGF1-R, mutation in the *KRAS* gene, or amplification of *ALK* and *KIT* genes occurs [11]. However, in 30–40% they depend on the selection of a clone cell with a point mutation in the *ALK* gene [8, 11]. Lorlatinib in pre-clinical studies showed activity against most known resistance mutations. Phase I and II studies confirmed its high efficacy in patients with advanced *ALK*-positive NSCLC, most of whom had previously been treated. Shaw et al. evaluated circulating DNA and tumour tissue samples from patients previously treated with ALK TKI, who took part in the phase II study [12]. samples were analysed from patients in five cohorts (Table 1): previously just crizotinib, previously crizotinib + chemotherapy or any other ALK TKI ± chemotherapy, two previous ALK TKI ± chemotherapy, and three previous ALK TKI ± chemotherapy. Samples were evaluated for the presence of mutations. A total of 75 mutations were detected, with G1202R being the most frequent (25%), followed by F1174 (15%), L1196M (15%), G1269A (11%), and I1171 mutations (8%). Responses were observed in 64% of patients whose samples contained more than one mutation in the ALK kinase domain. Also, 42% of patients without detectable mutation responded to lorlatinib. Mutation of G1202R was often observed in patients who earlier received 2 or 3 ALK TKI treatment lines [12].

Lorlatinib has been designed to overcome resistance to earlier therapy, but resistance may also occur when using this drug. Shaw et al. also demonstrated a new mechanism of resistance to this drug. In patients resistant to lorlatinib, they detected a double mutation (ALK C1156Y-L1198F), which if present, surprisingly, restores sensitivity to crizotinib [13].

Adverse effects

Hypercholesterolaemia (72%), hypertriglyceridaemia (39%), peripheral oedema (39%), and peripheral neuropathy (39%) were the most common side effects of lorlatinib [4]. In the Phase I study, level 2 CNS toxicity was found in the form of slowed speech and mental activity but also difficulty in finding words. It appeared in patients receiving 200 mg of lorlatinib once a day — dose-limiting toxicity (DLT) [4]. In the phase II study, third- and fourth-degree adverse effects related to treatment were found, which included hypercholesterolaemia (16%) and hypertriglyceridaemia (16%) [5]. No treatment-related deaths were reported. The toxicity of lorlatinib differs from that reported for other ALK TKIs. Hepatotoxicity (increased activity of aspartate transaminase or alanine transaminase) and gastrointestinal disorders (nausea, vomiting, diarrhoea) are mainly associated with other inhibitors and occur much less frequently with lorlatinib [3]. The side effects of lorlatinib do not affect the quality of life of patients. About 43% of treated patients report improved quality of life [5].

Brigatinib

Pharmacological characteristics of brigatinib

Brigatinib (AP26113, Alunbrig) is another oral TKI ALK. In preclinical studies with use of ALK-positive cell lines brigatinib showed a 12-fold greater potency than crizotinib [14]. It was characterised by a high

degree of selectivity, inhibiting only 11 kinases (from 289 evaluated), including ROS1, FLT3, mutant variants of FLT3 (D835Y), and EGFR (L858R). Whilst brigatinib demonstrated a lower anti-EGFR (including T790M resistance mutation), anti-IGF1R, and anti-INSR activity, it did not show activity against the MET pathway [14]. Compared to crizotinib, brigatinib showed an activity advantage and inhibitory profile against all assessed secondary *ALK* mutations, including G1202R [14]. After administration of a single oral dose (30–240 mg) the median time to maximum drug concentration (T_{max}) is 1–4 hours [16]. The mean elimination half-life in plasma is 25 hours, and hepatic excretion is the main route of drug elimination [15]. In *in vitro* studies, brigatinib has been shown to be metabolised by cytochrome CYP2C8 and CYP3A4, and, to a much lesser extent, by CYP3A5. Brigatinib is eliminated mainly through faeces [16].

Clinical trials with brigatinib

Phase I/II study

The multicentre phase I/II study was designed to determine the pharmacokinetics and the maximum tolerated dose, and to evaluate the side effects of brigatinib. In total 66 patients were enrolled with performance status 0–1 according to ECOG (Eastern Cooperative Oncology Group) scale, with measurable change according to RECIST 1.1 criteria. The study involved patients with asymptomatic CNS metastases.

Brigatinib was given orally at the doses of 30 mg, 60 mg, 90 mg, 120 mg, and 180 mg once daily. In the phase II study the doses of 90 mg, 180 mg, and 180 mg were used preceded by a seven-day initial period in which a dose of 90 mg was administered. In the phase II study patients were divided into five cohorts — patients with NSCLC and *ALK* gene rearrangement previously not treated with ALK TKI (cohort 1), patients with NSCLC and *ALK* gene rearrangement previously treated with crizotinib (cohort 2), patients with NSCLC and with T790M mutation in *EGFR* gene treated with TKI (cohort 3), patients with other cancers with concomitant disorders in *ALK* and *ROS1* gene (cohort 4), and patients with CNS metastases both treated and not treated with crizotinib [17].

The endpoint of the first part of this study was to determine the tolerated dose, and in the second part, the ORR. In the second part of the study a response was achieved by 100% of the patients in cohort 1, 74% of the patients in cohort 2 (31 out of 42 patients), none of the patients in cohort 3, 17% of the patients in cohort 4, and 83% of the patients in cohort 5 [17].

Phase II study

The study involved 222 patients from 71 sites randomly assigned (1:1) to arm A (brigatinib 90 mg once daily) and arm B (brigatinib 180 mg once daily with previous seven-day initial period in which a dose of 90 mg was used) [18]. Patients were stratified according to the CNS metastases (present or absent) and the type of response to previously used crizotinib (complete or partial response). The primary endpoint was ORR and the secondary endpoint was PFS and overall survival (OS). In arm A the ORR was 45% (97.5%, range from 34% to 56%), including one patient with complete response (CR), and in arm B 54% (97.5%, range from 43% to 65%), including four patients achieving CR. In arm A, PFS was 9.2 months, in arm B it reached 12.9 months [18]. The one-year OS rate was 71% and 80% in A and B arm, respectively.

Phase III study

From April 2016 to August 2017 at total of 275 patients in 124 sites were randomised (1:1) to the arm receiving crizotinib or brigatinib [19].

Patients were stratified according to the CNS metastases (present or absent). Patients in the brigatinib group received a 180-mg dose once daily (with a prior seven-day period with a dose of 90 mg) in 28-day cycles, and the patients in the crizotinib arm received 250 mg of the drug twice daily in 28-day cycles. In both arms the treatment was continued until the disease progressed. Patients in the crizotinib arm were allowed to cross-over to the brigatinib group after disease progression. The primary endpoint of the study was PFS. Secondary endpoints included the overall ORR and, in patients with measurable CNS, metastases.

The first analysis of the study showed the superiority of brigatinib over crizotinib in 12-month PFS (67% *vs.* 43%). ORR in the brigatinib arm was 71% *vs.* 60% in the crizotinib arm.

Efficacy in patients with metastases in the central nervous system

In the ALTA study the ORR in the group of patients with baseline measurable CNS metastases assessed by an independent expert committee reached 42% in arm A (11 out of 26 patients) and 67% in arm B (12 out of 18 patients) [18]. Among 39 patients with measurable lesions in CNS participating in a phase III clinical study, intracranial responses were achieved by 78% patients in the brigatinib group compared with 29% patients in the crizotinib group [19].

Adverse events

The most common adverse events reported during brigatinib treatment are summarised in Table 2.

In the ALTA study, 6% of patients experienced pulmonary adverse reactions in general (3% grade ≥ 3; including interstitial lung disease [ILD], pneumonia, and dyspnoea). These events were reported during the

Table 2. Adverse events of brigatinib [15, 19]

Study	Patients	AE G1–2	AE G3–4
I/II	71	Nausea (53%) Fatigue (43%) Diarrhoea (41%)	↑ lipase (9%) Dyspnoea (6%) Hypertension (5%)
ALTA	A — 112/B — 110	Nausea (33%/40%) Diarrhoea (19%/38%) Headaches (28%/27%) Cough (18%34%)	↑ CPK (3%/9%) Hypertension (6%/6%) Pneumonia (3%/5%)
ALTA-1L	137	Diarrhoea (49%) ↑ creatinine (39%) Nausea (26%) Cough (25%) Hypertension (23%)	↑ creatinine (16%) ↑ lipase (13%) Hypertension (10%)

↑ — elevated level; AE — adverse event; CPK — creatine phosphokinase

early treatment period (median time to onset — two days) [16, 18]. Early pulmonary adverse events also occurred in patients recruited to the dose escalation study — including three fatal cases (hypoxia, acute respiratory distress syndrome, and pneumonia). In addition, 2.3% of patients in ALTA study had pneumonia at a later stage of treatment, and in two patients it was grade 3 pneumonitis [16]. Interstitial lung disease or pneumonia was found in 4% of patients treated with brigatinib in the ALTA-1L study (2% in the crizotinib treated group) [19].

In 2017, the FDA approved the accelerated registration of the drug in the treatment of patients who have progressed after crizotinib treatment or with intolerance of this drug (breakthrough therapy).

Dacomitinib

Pharmacological characteristics of dacomitinib

Dacomitinib (PF-299804) is a strong, highly selective, second-generation oral TKI that irreversibly blocks EGFR/HER1, HER2, and HER4. It inhibits the tyrosine kinase activity by binding at the ATP binding site, which results in covalent modification of cysteine in the ATP binding cassette. The irreversible and highly selective properties of dacomitinib cause a persistent suppression of the tyrosine kinase receptor activity. Dacomitinib is absorbed orally with a median time of maximum concentration (T_{max}) in the range of five to 12 hours. The average half-life is 54 to 90 hours [21].

Clinical trials with dacomitinib

Phase I study

The phase I multi-centre study was designed to determine pharmacokinetics and maximum tolerable dose, and to assess the adverse effects of dacomitinib. It was attended by 57 patients previously treated with erlotinib or gefitinib with advanced NSCLC with ECOG 0–1 efficiency and normal organ function. Patients received dacomitinib at a dose of 0.5 to 60 mg once a day. A well-tolerated dose — recommended for further studies — was set at 45 mg once daily. In 33 patients the presence of *EGFR* gene activation mutation was confirmed, and in four patients T790M resistance mutation was detected. Out of 57 patients, 56% had ORR of whom four had partial response (PR) and 28 had stable disease (SD) [22].

Phase II study

The study involved 89 patients, 85% of whom were patients with confirmed mutation of EGFR gene activation (in 25 patients, deletion in 19 exon was detected, and in 20, insertion in exon 21). In 15% of patients, other types of mutations were identified; 15% of the studied population were patients without *EGFR* gene mutations. The average observation period was 24.8 months.

ORR in the whole population was 53.9%. In 47 patients (53%) PR was achieved, and in one CR — complete response — was noted. The percentage of PFS was 11.5 months. In the population of patients with confirmed activating mutation of *EGFR* gene, PFS was 18.2 months with no significant differences between patients with exon 19 deletion (16.6 months) and exon 21 insertion (18.3 months). PR was achieved in 34 out of 45 patients with mutation (76%).

The mean duration of treatment in the whole evaluated population was 9.2 months, and in the population with confirmed activation mutation it was 16.5 months. The most common side effects were diarrhoea (93%) and acne-like rash (78%). A promising improvement in PFS was observed in patients with EGFR gene activation mutation treated in the first line [22].

For comparison, in studies with reversible TKI, the first-generation PFS median in the population of patients with *EGFR* mutation was about 9–11 months [23, 24]. In a phase III study for afatinib, the PFS median was about 13 months in patients with mutation of *EGFR* gene activation [25].

Phase III study

From May 2013 to March 2015, in 71 centres, 452 patients were recruited, who were assigned in a ratio of 1:1 to one of two arms: the first arm was dacomitinib and the second was gefitinib (Table 3) [26]. Patients were stratified according to their race (Asian *vs.* non-Asian) and type of *EGFR* activating mutation (deletion in exon 19 *vs.* insertion in exon 21). In the first arm patients received dacomitinib 45 mg once a day in 28-day cycles, and in the second arm patients received gefitinib 250 mg once a day in 28-day cycles as well. In both arms the treatment was continued until progression of the disease. Treatment after progression was allowed in case of clinical benefit. The primary end-point was PFS. Secondary end-points incuded time to treatment failure (TTF) and OS.

In the arm with dacomitinib PFS was 14.7 months, and in the arm with gefitinib — 9.2 months.

In the group of patients with deletion of exon 19, 76% of patients with dacomitinib and 70% of patients with gefitinib received ORR.

In the group of patients with exon-21 mutation, this percentage was 73% in the arm receiving dacomitinib and 74% in the arm that received gefitinib.

The first analysis of the study in July 2016 showed that dacomitinib was superior to gefitinib in the first-line of treatment of patients with advanced NSCLC with activating mutation of *EGFR* gene in terms of PFS. The OS data did not reach maturity [26].

A second analysis in February 2017 showed an improvement in OS in favour of dacomitinib (34.1 months *vs*. 26.8 months) (Fig. 1).

In the group of patients with deletion in the 19 exon the mean OS was 34.1 months in the arm with dacomitinib; in the arm with gefitinib no OS was achieved.

In the group of patients with exon-21 mutation, the mean OS was 32.5 months in the dacomitinib arm and 23.2 months in the arm with gefitinib. In the analysis of subgroups concerning race, the mean OS in the

Table 3. Characteristics of patients — phase III study ARCHER 150 [26]

Data	Dacomitinib (n = 227)	Gefitinib (n = 225)
Age median (years)	62 (28–87)	61 (33–86)
< 65	133	140
> 65	94	85
Men	81	100
Women	146	125
ECOG		
0	75	62
1	152	163
Smoking status		
Never	147	144
Current	15	19
Prior	65	62
Exon		
19	134	133
21	93	92

ECOG — *Eastern Cooperative Oncology Group*

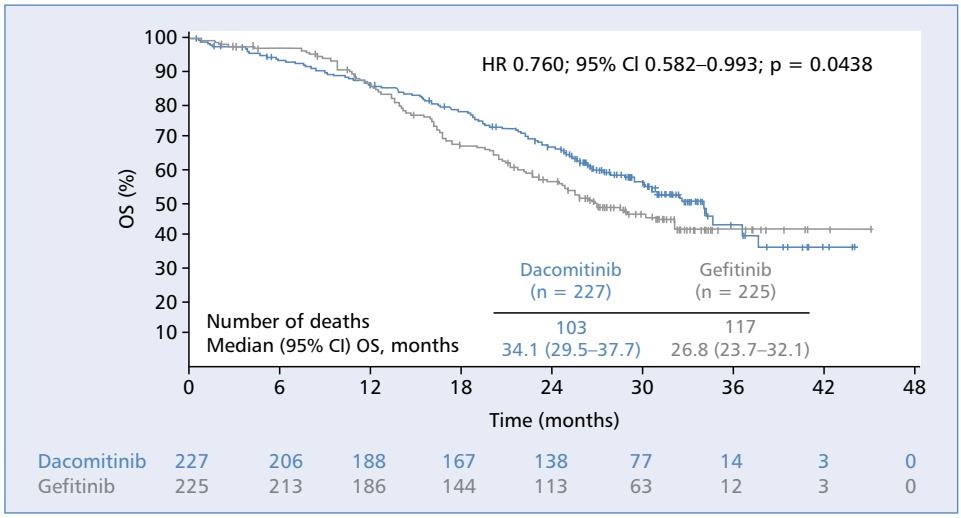

Figure 1. Overall survival time (OS) in the phase III ARCHER 150 study [26]

non-Asian population was 29.5 months in the arm of patients receiving dacomitinib, and 20.6 months in the arm of patients treated with gefitinib. In the Asian population these results were as follows: in the arm with dacomitinib OS was 34.2 months, and in the arm with gefitinib it was 29.1 months. During the 30-month observation period, the percentage of survivors was 56.2% in the arm with dacomitinib and 46.3% in the arm with gefitinib.

Dacomitinib is the first second-generation inhibitor that has significantly improved survival in advanced NSLCL patients with activating mutation of the *EGFR* gene [27].

Conclusions

The treatment of patients with NSCLC is still in progress. It concerns both deepening of knowledge about the cancer itself as well as the development of new therapeutic methods. The progress in basic sciences resulting in better understanding of cancer biology has contributed to the development of molecular target therapies. Their use in the first- and second-line of treatment has enabled us to achieve significant improvement in the prognosis of selected patients. The results confirm the legitimacy of searching for new, even more effective molecular target-oriented therapies, also effective in patients with developed resistance to earlier therapies or in the group of patients with metastases to the CNS and with previously very poor.

Lorlatinib is a third-generation ALK//ROS1 TKI, which showed significant activity in preclinical studies. It is active in patients with resistance to other ALK inhibitors (it showed anticancer effects in various resistance mutations, including the difficult-to-treat ALK G1202R mutation), and it is also characterised by the ability to penetrate the blood-brain barrier. Lorlatinib is a drug currently in clinical trials, so it has not been registered yet in any indication. The breakthrough therapy status granted the by the FDA was based on the efficacy and safety data from the Phase I and Phase II clinical trials. Recruitment for an open, randomised, bi-armed phase III CROWN clinical trial comparing lorlatinib with crizotinib in the first-line of treatment in patients with metastatic NSCLC with the presence of *ALK* gene rearrangement has been started.

Another ALK TKI is brigatinib. In 2017, the FDA approved the accelerated registration of the drug in the treatment of patients who had progression after crizotinib treatment or with intolerance of this drug (breakthrough therapy). Then, during the 19th WCLC and in the full-paper publication, preliminary results of the phase III ALTA-1L study were presented. Brigatinib compared to crizotinib significantly prolonged PFS in patients with ALK-"positive" NSCLC, previously untreated with ALK inhibitors. Brigatinib was also associated with an improvement of intracranial response rate.

Dacomitinib — a highly selective second-generation TKI that irreversibly blocks EGFR/HER1, HER2, and HER4 — is the first kinase inhibitor that has significantly improved survival in advanced NSCLC patients with mutation of *EGFR* gene activation. This review shows that dacomitinib should be considered as one of the standard drugs in the first line of treatment in patients with NSCLC with a confirmed mutation of *EGFR* gene activation.

References

1. http://www.who.int/en/news-room/fact-sheets/detail/cancer.
2. Ettinger DS, Akerley W, Bepler G, et al. Non-small cell lung cancer. J Natl Compr Canc Netw. 2010; 8(7):740–801.
3. Akamine T, Toyokawa G, Tagawa T, et al. Spotlight on lorlatinib and its potential in the treatment of NSCLC: the evidence to date. Onco Targets Ther. 2018; 11: 5093–5101, doi: 10.2147/OTT.S165511, indexed in Pubmed: 30174447.
4. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol. 2017; 18(12): 1590–1599, doi: 10.1016/S1470-2045(17)30680-0, indexed in Pubmed: 29074098.
5. Solomon B, Shaw A, Ou S, et al. OA 05.06 Phase 2 Study of Lorlatinib in Patients with Advanced ALK + /ROS1 + Non-Small-Cell Lung Cancer. Journal of Thoracic Oncology. 2017; 12(11): S1756, doi: 10.1016/j.jtho.2017.09.351.
6. https://www.drugs.com/clinical_trials/pfizer-s-next-generation-alk-ros1-inhibitor-lorlatinib-granted-breakthrough-therapy-designation-fda-17423.html.
7. https://clinicaltrials.gov/ct2/show/record/NCT03052608.
8. Millett RL, Elkon JM, Tabbara IA. Directed Therapies in Anaplastic Lymphoma Kinase-rearranged Non-small Cell Lung Cancer. Anticancer Res. 2018; 38(9): 4969–4975, doi: 10.21873/anticanres.12815, indexed in Pubmed: 30194140.
9. Nguyen TD, DeAngelis LM. Brain metastases. Neurol Clin. 2007; 25(4): 1173–1192, doi: 10.1016/j.ncl.2007.07.011, indexed in Pubmed: 17964030.
10. Collier TL, Normandin MD, Stephenson NA, et al. Synthesis and preliminary PET imaging of C and F isotopologues of the ROS1/ALK inhibitor lorlatinib. Nat Commun. 2017; 8: 15761, doi: 10.1038/ncomms15761, indexed in Pubmed: 28594000.
11. Krawczyk P. Mechanizmy oporności na leki z grupy IKT. Onkol Prakt Klin Edu. 2016; 2(supl B): B17.
12. Shaw A, Martini JF, Besse B, et al. Abstract CT044: Efficacy of lorlatinib in patients (pts) with advanced ALK-positive non-small cell lung cancer (NSCLC) and ALK kinase domain mutations. Cancer Research. 2018; 78(13 Supplement): CT044–CT044, doi: 10.1158/1538-7445.am2018-ct044.
13. Shaw AT, Friboulet L, Leshchiner I, et al. Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F. N Engl J Med. 2016; 374(1): 54–61, doi: 10.1056/NEJMoa1508887, indexed in Pubmed: 26698910.
14. Zhang S, Anjum R, Squillace R, et al. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016; 22(22): 5527–5538, doi: 10.1158/1078-0432.CCR-16-0569, indexed in Pubmed: 27780853.
15. Jain RK, Chen H. Spotlight on brigatinib and its potential in the treatment of patients with metastatic ALK-positive non-small cell lung cancer who are resistant or intolerant to crizotinib. Lung Cancer (Auckl). 2017; 8: 169–177, doi: 10.2147/LCTT.S126507, indexed in Pubmed: 29075144.
16. https://www.ema.europa.eu/documents/product-information/alunbrig-epar-product-information_pl.pdf.
17. Gettinger S, Bazhenova L, Langer C, et al. Activity and safety of brigatinib in ALK -rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. The Lancet Oncology. 2016; 17(12): 1683–1696, doi: 10.1016/s1470-2045(16)30392-8.

18. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. J Clin Oncol. 2017; 35(22): 2490–2498, doi: 10.1200/JCO.2016.71.5904, indexed in Pubmed: 28475456.
19. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018; 379(21): 2027–2039, doi: 10.1056/NEJMoa1810171, indexed in Pubmed: 30280657.
20. http://www.ascopost.com?News/59297
21. Janne PA. Boss DS. Camididge DR Phase I Dose-escalation of the Pan-HER Inhibitor PF299804, in Patients with Advanced Malignant Solid Tumors Clin Cancer Res. 2011; 17(5): 1131–1139.
22. Jänne P, Ou SH, Kim DW, et al. Dacomitinib as first-line treatment in patients with clinically or molecularly selected advanced non-small-cell lung cancer: a multicentre, open-label, phase 2 trial. The Lancet Oncology. 2014; 15(13): 1433–1441, doi: 10.1016/s1470-2045(14)70461-9.
23. Mok TS, Wu YL, Thongprasert SI, et al. Thongprasert S. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361(10): 947–957.
24. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353(2): 123–132, doi: 10.1056/NEJMoa050753, indexed in Pubmed: 16014882.
25. Sequist L, Yang JH, Yamamoto N, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. Journal of Clinical Oncology. 2013; 31(27): 3327–3334, doi: 10.1200/jco.2012.44.2806.
26. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017; 18(11): 1454–1466, doi: 10.1016/S1470-2045(17)30608-3, indexed in Pubmed: 28958502.
27. Mok TS, Cheng Y, Zhou X, et al. Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non-Small-Cell Lung Cancer and EGFR-Activating Mutations. J Clin Oncol. 2018; 36(22): 2244–2250, doi: 10.1200/JCO.2018.78.7994, indexed in Pubmed: 29864379.

VIA MEDICA

REVIEW ARTICLE

Piotr Potemski[1], Joanna Połowinczak-Przybyłek[1], Rafał Wójcik[2], Marcin Kaczor[3]

[1]The Department of Chemotherapy, Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz; Chemotherapy Clinic, Medical University of Lodz, Poland
[2]Aestimo, Krakow, Poland
[3]Jagiellonian University Medical College, Krakow, Poland

Critical appraisal of clinical trials in oncology — part II

Address for correspondence:
Prof. dr hab. n. med. Piotr Potemski
Klinika Chemioterapii Nowotworów
Uniwersytet Medyczny w Łodzi;
WWCOiT im. M. Kopernika w Łodzi
e-mail: piotrpo@mp.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 3, 158–166
DOI: 10.5603/OCP.2019.0013
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

The article is the second part of papers presenting informations useful for an independent analysis of the value of published results of clinical trials in oncology. Based on selected examples of clinical trials, a few attempts of critical appraisal of clinical trial assumptions, construction, and interpretation of their results are given. Several non-inferiority trials are discussed. The paper provides examples of publications in which post hoc analyses, grouping of variables, and multiple comparisons were made. Examples of research with a controversial selection of patients and a comparator, as well as studies whose clinical significance of the obtained results is questionable are presented. The aim of our work is to draw the reader's attention to selected essential elements of clinical trials and the way of presenting their results in order to facilitate practitioners in the independent evaluation of available publications and rational use of clinical trial results in everyday practice in the future.

Key words: oncology, clinical trials, critical appraisal, publication analysis, research methodology, interpretation of results

Oncol Clin Pract 2019; 15, 3: 158–166

Introduction

The first part of the publication presented general information helpful for independent analysis of the value of published results of clinical trials in oncology. Unfortunately, the description of the methodology is often presented in publications in a very short form, and more details can be found only after reading the protocol, which is not always available. In addition, the time the practitioner can devote to critically evaluate a new publication is usually very limited. All this means that it is quite difficult for the reader, who is a practitioner rather than a specialist in the field of clinical trial methodology, to systematically assess all the elements that make up the reliability of a given study, even after a very careful reading of the publication resulting from a clinical trial. This paper provides practical examples of interpretation of selected clinical trials. For obvious reasons, the analyses presented cannot be a comprehensive assessment of the results of these studies but are only an attempt to draw the reader's attention to selected, but in the authors' opinion very important, elements that may affect the interpretation of the published results and their impact on clinical practice.

Non-inferiority studies

Due to a different methodology than that utilised in commonly-used superiority studies, the non-inferiority design usually causes inconvenience for clinicians. It assesses whether an intervention is not inferior, in terms of clinical efficacy, than the current standard of treatment. The basic element subjected to critical evaluation during interpretation of this type of study is the assumed delta value, determining the acceptable difference in the clinical effectiveness of interventions being compared. It can be defined, for

example, by determining the magnitude of maintaining the clinical effectiveness of the current treatment standard, based on the results of a historical study comparing the current standard with symptomatic treatment (ASPECCT study) or determining the upper limit of the confidence interval based on the value of a clinically acceptable difference of effects adopted as part of the consensus (e.g. IDEA study). When interpreting the results of this kind of studies, it is worth paying attention to how large differences can be assumed that are still considered acceptable.

ASPECCT study

The ASPECCT study was a prospective, non-inferiority, phase III clinical trial planned to prove that panitumumab monotherapy in patients with metastatic colorectal cancer (CRC), who previously received chemotherapy, could result in at least half of the efficacy of cetuximab expressed by increased overall survival (OS) as compared to the best supportive care (BSC) demonstrated in a historic phase III study [1]. Such a defined delta value demonstrating non-inferiority seems to be a very safe assumption, which is easy to confirm in clinical trial. The study that was referred to in this assumption was the CO.17 study, the results of which, in a population of patients without *KRAS* mutation, were published in 2008 [2]. In this study the hazard ratio (HR) for death in the cetuximab group compared to only symptomatic treatment was 0.55 (95% CI 0.41–0.74), and median OS were 9.5 and 4.8 months, respectively. In total, 1010 patients were included in the ASPECCT study, and in the first scheduled analysis the assumption was proven, showing that panitumumab maintained from 81.9 to 129.5% of the effect of cetuximab on OS.

IDEA study

The IDEA (International Duration Evaluation of Adjuvant Therapy) study is a prospectively planned, pooled analysis of individual data of patients with colon cancer participating in six randomized trials, comparing the efficacy of three-month adjuvant oxaliplatin chemotherapy (FOLFOX-4 or modified FOLFOX-6 or CAPOX) with standard treatment lasting half a year [3]. The reason for planning such a study was the desire to reduce adjuvant therapy-related toxicity (mainly polyneuropathy) that may adversely affect the activity and quality of life of radically treated patients.

The primary endpoint was DFS (disease-free survival) in a modified intent-to-treat population (randomised patients who received at least one dose of chemotherapy), which was achieved by a total of 12,834 out of 13,025 randomised patients. The delta value was set as the upper limit of 95% CI HR_{DFS} of 1.12. Therefore, if 95% CI HR_{DFS} exceeded 1.12, the null hypothesis cannot be rejected, which would mean that the shorter duration treatment is worse than the assumed value than the standard treatment. According to the authors of the study, this delta value was estimated to translate into a predicted reduction in a DFS rate after three years by a maximum of 2.7 percentage points, and this value was considered acceptable by the researchers. As a reminder, in another study in CRC (MOSAIC), which established a value of FOLFOX adjuvant chemotherapy, patients with stage III disease had a DFS rate of 72.2% after three years, compared to 65.3% in those receiving fluorouracil with calcium folinate [4]. More important, however, is the effect of FOLFOX expressed in HR_{DFS}, which in the MOSAIC study was 0.76 (95% CI: 0.62–0.92), which means that HR for relapse decreased by 24%, and the "true" value of this reduction (i.e. the value transferred to the so-called general population) was between 8% and 38%. The delta value adopted in the IDEA study corresponds to maintaining about 60% of the effect in HR_{DFS} found for the comparison of FOLFOX to fluorouracil with calcium folinate in patients with stage III CRC participating in the MOSAIC study. In the IDEA study, according to the randomisation design in the primary studies used, interventions were compared only for the duration of chemotherapy, but not the type of chemotherapy.

In the modified intent-to-treat population HR_{DFS} for treatment lasting three months *vs*. six months amounted to 1.07 (95% CI 1.0–**1.15**), the assumed value of the statistically significant level of p-value for the hypothesis of non-inferiority three-month treatment was 0.11, and the p-value for the superiority hypothesis of six-month treatment was 0.045. This means that the primary endpoint was not met, and it was not proven (with the adopted delta value) that the shorter treatment is not inferior to the standard one. There are occasionally assessments of the results of this study based on numerical values of survival rates after three years — 74.6% and 75.5%, respectively. According to this assessment, the difference in a DFS rate (0.9 percentage points) is too small to be clinically relevant. This interpretation of IDEA research results shows a complete misunderstanding of statistical methodology and is entirely incorrect.

Moreover, pre-planned subgroup analyses were of an exploratory nature and cannot be interpreted in isolation from primary results of the study. It was found that probably the type of chemotherapy (FOL-

FOX or CAPOX) affects the effectiveness of three--month treatment (p for the interaction test was 0.006, and after the adjustment for multiple testing it was 0.02). In the group of 5071 patients receiving CAPOX HR_{DFS} amounted to 0.95 (95% CI: 0.85–**1.06**), which would confirm the assumptions of non-inferiority. Unfortunately, as previously mentioned, in the included studies no randomisation was made depending on the type of chemotherapy, or even randomisation was not stratified according to the type of chemotherapy. These factors mean that a result related only to the CAPOX scheme can be completely accidental, especially since it is difficult to find medical justification for such an observation.

Subgroup analyses and multiple comparisons not previously planned

As presented in the first part of the publication, randomisation is a very important element of a properly designed and conducted clinical study. It ensures, with a sufficiently large population, an even distribution of various, also unknown, confounding factors. The lack of randomisation or partial loss of its effect, e.g. as a result of post hoc analyses of previously unplanned subgroups of patients, means that compared groups may significantly differ in the distribution of other significant prognostic features.

IDEA study

In the IDEA study discussed above, subgroups were initially defined depending on the T (T1–3 and T4) and N (N1 and N2) feature, and none of the assumptions of non-inferiority of treatment lasting three months were shown in any of them. However, when analysing post hoc results, two categories of recurrence risk were created: low (T1–3N1) and high (T4 or N2). In the low-risk category (7471 patients) the assumption of non-inferiority regardless of the type of chemotherapy was confirmed at borderline (HR_{DFS} = 1.01, 95% CI: 0.90–**1.12**); similarly it was confirmed in the group of patients (N = 2,852) receiving CAPOX and classified as low risk (HR_{DFS} = 0.85, 95% CI: 0.71–**1.01**). In all other groups, i.e. high risk, regardless of the type of chemotherapy, or FOLFOX-treated low-risk patients, non-inferiority assumptions could not be demonstrated. It should be taken into account that the evaluation depending on these categories was not planned before, and it was performed only after analysing the obtained results. This means that in these subgroups the unknown additional factors may play an important role, and due to this the results of post hoc analyses cannot be considered as formal proofs used to infer real differences in the effectiveness of interventions. In the opinion of the authors of this work, the only potentially useful suggestion resulting from these analyses may be the possibility to shorten the duration of CAPOX chemotherapy to three months in patients with T1––3N1 CRC in the case of poor treatment tolerance, as an alternative to reducing the oxaliplatin dose or its withdrawal and continuing therapy with fluoropyrimidine alone.

ASPECCT study

Even better, the problem of multiple comparisons and random results considered "statistically significant" is illustrated in an article published in 2016, which presents the updated results of the ASPECCT study and, among others, post hoc analysis depending on previous treatment with bevacizumab [5]. It was found that in a group of 258 patients who were previously treated with bevacizumab OS was longer when they received panitumumab, not cetuximab. Medians OS were 11.3 and 9.8 months, respectively (HR = 0.75, 95% CI: 0.58–0.97). This observation has led to attempts to promote panitumumab rather than cetuximab as the drug of choice in patients previously exposed to bevacizumab. This raises the question of how to explain the advantage of panitumumab over cetuximab in individuals who have previously been treated with bevacizumab, when the biological mechanism of action of both drugs is very similar. This is a good example of misinterpretation of observation results, the nature of which is probably accidental and should not be the basis for a change in clinical practice. Obviously, in such situations, the statistically significant p-value should be lower than the usual one (< 0.05) because it must take into account unplanned hypothesis multiple testing used in post hoc analyses (Bonferroni correction).

Presenting the results of previously unplanned comparisons means that many similar ones were most probably carried out in other subgroups, but only some of them were selected because the more post hoc analyses are carried out, the more likely it is that the outcome of any of them will be completely randomly "statistically significant".

A study "showing" the importance of the astrological zodiac signs in medicine

Very instructive examples of the apparent demonstration of non-existent relationships are two works published by their authors just to show readers the dangers resulting from making multiple comparisons and grouping post hoc variables [6, 7].

In the first one, the relationships between astrological zodiac signs and the 223 most frequent reasons for hospitalisation of the inhabitants of Canada were evaluated [6]. A group of over 10 million people was randomly divided into two groups: a cohort in which possible relationships were tested and an independent validation cohort. Two zodiac signs were found to be associated with a higher risk of hospitalisation compared to the remaining 10. In the validation cohort, the relationship between the two signs and the individual causes of hospitalisation was examined, and it was found that people born under the sign of Leo were significantly more frequently (p = 0.0447) hospitalised due to gastrointestinal bleeding, and those born under the sign of Sagittarius significantly more often (p = 0.0123) due to humerus fracture, compared to people born under the other signs of the zodiac. Obviously, after introducing adjustment for multiple testing, these apparent relationships disappeared.

Another study investigated the relationship between the zodiac sign and prognosis after myeloablative chemotherapy and allogenic haematopoietic stem cell transplantation in patients with chronic myelogenous leukaemia [7]. The survival probabilities of at least five years were analysed in a group of 626 patients depending on their zodiac sign, and numerical but not statistically significant differences were found. However, when individuals born under the sign of Aries, Taurus, Gemini, Leo, Scorpio, or Capricorn (a total of 317 patients) were separated and compared with the remaining group (309 patients), the difference was statistically significant (five-year survival 58% *vs.* 48%; p = 0.007). Moreover, after a multivariate analysis that took into account the possible impact of other known prognostic factors, the results of treatment of patients born under one of the zodiac signs mentioned above were still significantly better than in the remaining patients (p = 0.005). The authors concluded that this is an example of "proving" a non-existent correlation, and the observed "significant" dependencies are the result of grouping post hoc variables in order to obtain the greatest and "statistically significant" difference.

COU-AA-302 study

An example of a proper interpretation of the possible impact of multiple testing in relation to survival outcomes is the adoption of another threshold of statistical significance for the results of pre-planned, stepwise analyses of randomised clinical trials. For example, in the phase III COU-AA-302 study, which compared abiraterone acetate in combination with prednisone to placebo-prednisone combination in patients with metastatic castration-resistant prostate cancer not previously treated with docetaxel, the two primary endpoints were: radiographic progression-free survival (rPFS) and OS. A typical p-value of 0.05 was therefore divided into both endpoints by default — the statistical significance of the difference in rPFS required that the p-value should be less than 0.01, and in the case of OS — less than 0.04 [8].

It was planned that the OS assessment would be conducted in several stages (interim analyses) — after the occurrence of 15%, 40%, and 55% of the number of deaths required for the final analysis, respectively, and final analysis after the occurrence of at least 773 deaths (1,088 patients were included in the study). Due to multiple testing of drug effects on OS (with data cut-offs at different time points), the correction of borderline p-values required to establish statistical significance found in these stepwise analyses of differences was applied in accordance with the procedure described by O'Brian and Fleming. The first publication contained the final result of the rPFS analysis, which found a statistically significant difference between abiraterone and placebo (HR = 0.55, 95% CI: 0.45–0.62, p < 0.001) and the result of interim OS analysis after 43% of the required 773 events. It was found that the HR_{OS} was 0.75 (95% CI: 0.61–0.93, p = 0.01). Although the p-value was less than the required 0.04, only the adjusted p-value of 0.001 or less was determined to indicate the statistical significance of the OS difference in this stepwise analysis. The result of the next published interim analysis carried out after 56% of deaths was also not statistically significant (HR = 0.79, 95% CI: 0.66–0.95, p = 0.0151, required adjusted p-value = 0.0035) [9]. Only the final OS analysis after 96% of the 773 deaths revealed the effect of the drug on OS prolongation (HR 0.81, 95% CI 0.70–0.93, p = 0.0033), i.e. it was allowed to meet the second co-primary endpoint [10].

Selection of patients and comparators

The correct patient selection, appropriate to carry out the planned intervention, is an indispensable element of a well-designed and conducted study, and also allows extrapolation of the outcomes to a population that will be treated in real-life clinical practice. The use of a proper comparator, which is a key element of a well-conducted clinical trial, implies the use of therapy that is consistent with current clinical practice and generally accepted recommendations and guidelines, including their continuous evolution, especially in a field developing as rapidly as oncology. In-

appropriate selection, contrary to commonly accepted recommendations, makes it impossible to accept study conclusions as reliable (external credibility). An example of a recently published trial with highly controversial patient selection is the CARMENA study.

CARMENA study

The aim of the non-inferiority phase III CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) study published in 2018 was to show that not performing nephrectomy in patients with metastatic renal cell carcinoma (mRCC) prior to sunitinib treatment is not inferior to such therapy with previous nephrectomy [11]. The primary endpoint was OS, and randomisation was stratified, among others, by prognostic categories. The results of the CARMENA study are fairly widely interpreted as being likely to change clinical practice, as it has been shown that not performing cytoreductive nephrectomy is non-inferior (HR_{OS} = 0.89; 95% CI: 0.71–1.10; non-inferiority criterion: upper limit of 95% CI not higher than 1.20).

However, while analysing the significance of the obtained result and its potential impact on clinical practice, the key limitation of this study should be remembered, which was the selection of patients. The study included patients meeting the criteria of intermediate or poor prognosis according to the MSKCC (Memorial Sloan Kettering Cancer Centre), and as many as 43% of patients participating in CARMENA study were assigned to the category of unfavourable prognosis. Until recently, in patients included in the category of unfavourable prognosis, the only drug for which phase III study showed a slight effect on OS prolongation was temsirolimus, a drug currently being reimbursed in such patients, also in Poland [12]. There are also no reliable data from a randomised study confirming the effect of sunitinib, used in CARMENA study, on OS in patients with unfavourable prognosis. In addition, nephrectomy is generally not performed or recommended in such patients, and in the aforementioned phase III study with temsirolimus, no beneficial effect of this procedure (sometimes performed a long time prior to randomisation) was observed on the efficacy of mTOR inhibitor. For these reasons, allowing inclusion in the study assessing the impact of abandoning nephrectomy the patients with poor prognosis category and treating them with sunitinib should be considered as not justified by existing medical knowledge. The use of sunitinib but not temsirolimus in some centres in patients with poor prognosis cannot be considered as practice in line with Evidence-Based Medicine.

The results of the CARMENA study were obtained in all patients enrolled, and those with an unfavourable prognosis had a significant influence on the final study results. In this group of patients neither nephrectomy nor sunitinib could affect the primary endpoint. With this assumption, it would not be difficult to prove non-inferiority of not performing nephrectomy in high-risk patients. An indication that seems to support this hypothesis may be the results for each prognostic group separately. In the group of unfavourable and intermediate prognosis, HR_{OS} were 0.86 (95% CI: 0.62–**1.17**) and 0.92 (95% CI: 0.68–**1.24**), respectively. As can be seen, only in the unfavourable prognosis group did the obtained result meet the accepted non-inferiority criterion (upper limit of 95% CI not greater than 1.20). Obviously, this cannot be considered as evidence but only a premise indicating the correctness of the given interpretation.

The statistical analysis carried out in the intent-to-treat (ITT) population assumes the evaluation of the results of all randomised patients, regardless of whether they received the assigned intervention or not. The interpretation of the result of the CARMENA study should also take into account the fact that 16 patients in the group of 226 included in the nephrectomy arm (7%) did not have it, and 38 of 224 subjects randomised to the arm with only systemic therapy (17%) underwent nephrectomy. This reduces the differences between the arms and facilitates the demonstration of non-inferiority in the ITT population. Finally, the original plan assumed the inclusion of 576 patients and the evaluation after 452 deaths, but as a result of the unsatisfactory recruitment rate the study was discontinued after including 450 patients, and the final results were published after the occurrence of 326 deaths.

CheckMate 214 study

The problem of selection of the comparator and target population was also encountered in the phase III CheckMate 214 study, in which the combination of nivolumab with ipilimumab in patients with mRCC was evaluated, and sunitinib was used as a comparator [13]. Whereas in the case of patients with a favourable or intermediate prognosis such a comparator does not raise any doubts; in the case of patients included in the category of unfavourable prognosis it is difficult — for reasons discussed earlier — to be considered as optimal. Such patients accounted for as much as 21% of the population in which the primary endpoints were assessed, i.e. objective response rate, PFS, and OS. The p-value of the statistical significance 0.05 was divided into: 0.001 (objective response rate), 0.009 (PFS), and

0.04 (OS). Patients were included in the study regardless of the prognostic category, but the assessment of primary endpoints was only planned for patients with an intermediate or unfavourable prognosis. Secondary endpoints included: objective response rate (ORR), PFS and OS in randomized patients (IT population), and the frequency of adverse events in patients who received treatment. An exploratory analysis was planned only in a group of 249 patients with a favourable prognosis (21% of the randomised population).

Regarding the primary endpoints, there were differences in ORR and OS in favour of immunotherapy, but not in PFS ($p = 0.03$). In the randomised population, no significant difference was found in any of the three secondary efficacy endpoints. This means that the inclusion of patients from the favourable prognosis group abolished the beneficial effect of immunotherapy with respect to response rate and OS. The results of an exploratory efficacy analysis in a favourable prognostic group are very worrying — there has been a reversal of the influence of immunotherapy and comparator to the detriment of experimental treatment. The response rate was 29% *vs.* 52% ($p < 0.001$), $HR_{PFS} = 2.18$ ($p < 0.001$), and $HR_{OS} = 1.45$ ($p = 0.27$, with only 37 deaths).

An obvious interpretation of the study results indicates that the benefit of immunotherapy is limited only to patients in the intermediate or poor prognosis category (with explicit reservation regarding external reliability due to the use of a suboptimal comparator in the latter group). However, it should be noted that only one of the six factors of unfavourable prognosis according to the International Metastatic Renal Carcinoma Database Consortium (IMDC) classification: Karnofsky performance status 70, time from diagnosis of cancer to randomisation shorter than one year, anaemia, corrected calcium concentration in serum above 10 mg/dl, neutrophilic granulocytosis, and thrombocythaemia, was associated with a benefit in immunotherapy. Inevitable doubts therefore arise as to whether this relationship is true for each of these mentioned factors that are so different, and whether the benefit of immunotherapy depends on the number of poor prognosis factors. Unfortunately, the publication of CheckMate 214 results does give any answers these question. Among 667 patients belonging to the intermediate-risk group, no analyses were performed that could clarify these doubts.

Another surprising choice was the use of only a combination of anti-CTLA4 and anti-PD1 antibody in the experimental arm, but not anti-PD1 monotherapy. This could be due to the desire to obtain the best direct effect (ORR was one of the primary endpoints). This does not undermine the value of the combination itself, but raises the question, however, of whether anti-PD1 monotherapy would not be equally effective and less toxic as well. This question can be considered as justified especially in the context of the final results of the previously launched CheckMate 025 study, published at the end of 2015, in which in previously treated patients nivolumab was used with good results. Such a doubt was raised by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) as justification for a surprising primary negative opinion regarding the registration of this combination in patients with kidney cancer.

SOLO3 study

It is also bewildering to select a comparator in the ongoing phase III SOLO3 study, in which olaparib is compared to single-agent chemotherapy in women with recurrent (at least two earlier lines of chemotherapy containing a platinum compound) still platinum-sensitive (progression later than six months after the end of the last chemotherapy) ovarian cancer with the presence of germline *BRCA* mutation [14]. The planned primary study endpoint is ORR. The comparator is the investigator's choice between paclitaxel, liposomal doxorubicin, topotecan, and gemcitabine.

As a reminder, a commonly accepted standard treatment for such patients is platinum-based chemotherapy and not monotherapy with any of the drugs mentioned above. In addition, the choice of the primary endpoint is also difficult to consider to be appropriate and clinically important. Considering these reservations, it is difficult to imagine that the result of this study could be useful in clinical practice.

20100007 study

If the use of placebo, or only BSC, as a comparator is common practice when there is no other therapeutic option with proven efficacy (usually the last treatment line), or the intervention tested and placebo as a comparator are added to the current standard (add-on), the use of placebo or only BSC in a situation where there are other therapies with previously demonstrated efficacy should always raise ethical concerns. The aim of this phase III study published in 2016 was to demonstrate that panitumumab affects OS prolongation compared to BSC in previously systemically treated patients with metastatic CRC without mutation in exon 2 of the *KRAS* gene [15]. There would be nothing surprising in the study design if not for the fact that the recruitment of patients was carried out between

November 2011 and July 2013, offering BSC as a comparator. This contradicted common knowledge about the efficacy of cetuximab in the treatment of patients with metastatic CRC. In the phase III study published in 2007 (the recruitment started in January 2004) and in which the value of panitumumab was for the first time evaluated in comparison to BSC, the authors highlighted that the project assumed from the beginning the possibility of changing the study arm in the control group after disease progression (cross-over) due to the "previously known activity of panitumumab and cetuximab" [16]. In addition, the design of this study with PFS as the primary endpoint and assumed cross-over meant that during the registration, the manufacturer was required to plan and conduct a non-inferiority study comparing panitumumab with cetuximab, because since 2007 the effect of cetuximab on OS prolongation has been known in comparison to BSC. Both antibodies, i.e. panitumumab and cetuximab, have been registered for the treatment of patients with chemoresistant metastatic CRC by both the US Food and Drug Administration and the EMA. In the European Union cetuximab was authorised in 2004 and panitumumab in 2007 (already taking into account the state of the *KRAS* gene). In 2008, the registration of cetuximab was modified, taking into account the state of the *KRAS* gene. In February 2010, recruitment to the previously discussed non-inferiority ASPECCT study was started, in which OS was the primary endpoint. How then, a few years after the first registration of both drugs, was it possible to conduct a clinical trial in which half of the patients included in the study received only BSC or a suboptimal procedure? Obviously, in the 20100007 study cross-over to panitumumab in the control group after disease progression was not assumed, and yet such an option was in the study, which was conducted during the period when there was no data confirming the effect of anti-EGFR drugs on OS.

Is every statistically significant difference also clinically relevant?

An element of critical evaluation of clinical trials in oncology should always be an answer to the question of whether the statistical significance obtained in a study is of practical significance and whether it is enough to change clinical practice. This issue raises a lot of controversy, because the assessment of how much of the benefit from a PFS or OS extension can be considered clinically relevant is extremely subjective. The discussion about this began, among other things, because there was a tendency to design commercial studies carried out on very large groups of patients, in which very small differences in efficacy could be demonstrated, but still achieving a level of statistical significance. Taking into account the fact that the primary endpoint of these studies was PFS, it was difficult to translate these results into clinical practice, especially considering the higher toxicity and significant cost of new drugs.

NCIC CTG PA.3 and VELOUR studies

The phase III NCIC CTG PA.3 study showed that the combination of gemcitabine and erlotinib in patients with advanced pancreatic cancer statistically significantly prolongs OS [17]. Although it was the first phase III study indicating advantage of combining gemcitabine with another drug, a fairly common perception of the clinical relevance of this study was far from enthusiastic, and this study became a classic example of a statistically significant but clinically meaningless result. The reason for this was primarily the low numerical difference in OS — HR had a value of 0.82 (95% CI: 0.69–0.99), the median OS 6.24 *vs.* 5.91 months, and 12-month survival rate was 23% *vs.* 17%. The large number of patients included in the study (569 people) meant that the absolute difference in the number of deaths between the arms of eight cases translated into statistical significance in the log-rank test. Especially underlined by the commentators was the difference in medians amounting to only 0.33 months. In addition, an increased frequency of some adverse events, e.g. diarrhoea and skin lesions, was observed in the experimental arm.

Assessment of the NCIC CTG PA.3 study value tested only from the perspective of difference in medians, although easy to communicate, is obviously somewhat simplified because it covers only one time point on survival curves. A better, although non-intuitive, measure is HR for death, in which an 18% reduction is already more clinically promising. For comparison, aflibercept, a drug currently being reimbursed in Poland in second-line treatment for patients with metastatic CRC added to FOLFIRI chemotherapy regimen in the phase III VELOR study, reduced HR for death by 18% (HR 0.817, 95% CI 0.713–0.937). The difference in medians was 1.44 months, and the probability of 24-month survival was 28% *vs.* 19% [18]. Demonstration that such a difference is statistically significant at the p level of 0.0032 was possible due to the inclusion of up to 1,226 patients in the study. Then, several reports were published to dispel doubts as to whether the difference in prognosis found in the VELOUR study is clinically relevant. One year after the original publication, extrapolating the obtained data

beyond the duration of the study using mathematical methods, the mean survival times of patients from both arms were estimated in the perspective of 15 years, stating that the difference between them is 4.7 months, which seems to have made an improved impression on the readers of that time than the difference in medians of 1.44 months [19]. Another attempt, the result of which was announced in print in 2014, consisted of making post hoc analyses and, as a result, extracting the subgroups referring to the "greater" benefit from experimental treatment [20]. It was found that patients in very good performance status (PS 0) with any number of distant metastases and patients in good condition (PS 1) having metastasis only in one location have a median OS greater by 3.1 months if they received aflibercept. Obviously, such analyses can generate research hypotheses, but certainly they do not allow the transfer of the results obtained in this way to the so-called general population. The value of post hoc analyses based on variable grouping has already been discussed in this article. It should be mentioned here that such actions are unfortunately used to obtain the greatest possible difference in the median of survival, which facilitates obtaining more favourable results of the cost-effectiveness analysis carried out as part of the process of reimbursement application. It is very likely that the subgroups extracted in this manner may not have any real predictive value.

NO16966 study

An example of a study that, at least some countries (e.g. in the USA), influenced the change of clinical practice despite seriously doubting the real value of the obtained results, was a phase III trial evaluating the benefit of adding bevacizumab to oxaliplatin-containing chemotherapy in the first line of treatment of patients with metastatic CRC [21]. The primary endpoint was PFS, and patients who received either FOLFOX-4 or XELOX chemotherapy with bevacizumab showed longer PFS (HR = 0.83, 95% CI: 0.72–0.95, median PFS: 9.4 *vs.* 8.0 months). The difference was statistically significant at p value = 0.0023, and it was possible to demonstrate it due to the sample size of 1,401 patients. Naturally, there was no OS benefit due to the use of antibody.

Doubts about the clinical significance of the results of some studies are the reason that ESMO (European Society for Medical Oncology) proposed the values of differences in individual endpoints depending, among others, on a prognosis that may be considered clinically significant [22]. The review of randomised clinical trials published between 2011 and 2015 regarding systemic treatment of patients with breast cancer, NSCLC, CRC, or pancreatic cancer included 277 studies [23]. In 138 of these studies, statistically significant differences between experimental therapy and the comparator were presented; however, after using the ESMO criteria of clinical significance, the results only 43 (31%) out of 138 studies were considered to be statistically significant.

Summary

In this analysis, the authors focused on selected issues, illustrating them with examples of specific clinical trials. Non-inferiority studies have been discussed because this type of clinical trial usually poses a lot of problems to readers, which is associated with a completely different methodology compared to studies that aim to demonstrate the superiority of one intervention over another. Examples of publications with post hoc analyses, grouping of variables, and multiple comparisons are given. Examples of clinical trials are presented, understanding and interpretation of which are impossible without paying attention to doubts about the characteristics of patients being included or the selection of a comparator. An extreme example of research with results that are difficult to transfer to clinical practice are those in which the control group is treated suboptimally, i.e. less effectively than is possible. Fortunately, there are not many of such studies, but more often there are clinical trials in which doubts relate to some of the patients included in them. Finally, examples of studies raising doubts about the so-called clinical relevance of the results obtained are given.

The authors hope that two publications prepared in cooperation of medical statisticians and oncologists will make easier for readers to interpret the available publications and thus rationally use the results of clinical trials in everyday practice.

References

1. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014; 15(6): 569–579, doi: 10.1016/S1470-2045(14)70118-4, indexed in Pubmed: 24739896.
2. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359(17): 1757–1765, doi: 10.1056/NEJMoa0804385, indexed in Pubmed: 18946061.
3. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med. 2018; 378(13): 1177–1188, doi: 10.1056/NEJMoa1713709, indexed in Pubmed: 29590544.
4. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med.

2004; 350(23): 2343–2351, doi: 10.1056/NEJMoa032709, indexed in Pubmed: 15175436.
5. Price T, Kim TW, Li J, et al. Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild-type KRAS exon 2 metastatic colorectal cancer. Eur J Cancer. 2016; 68: 51–59, doi: 10.1016/j.ejca.2016.08.010, indexed in Pubmed: 27716478.
6. Austin PC, Mamdani MM, Juurlink DN, et al. Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health. J Clin Epidemiol. 2006; 59(9): 964–969, doi: 10.1016/j.jclinepi.2006.01.012, indexed in Pubmed: 16895820.
7. Szydlo RM, Gabriel I, Olavarria E, et al. Sign of the Zodiac as a predictor of survival for recipients of an allogeneic stem cell transplant for chronic myeloid leukaemia (CML): an artificial association. Transplant Proc. 2010; 42(8): 3312–3315, doi: 10.1016/j.transproceed.2010.07.036, indexed in Pubmed: 20970679.
8. Ryan CJ, Smith MR, de Bono JS, et al. COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013; 368(2): 138–148, doi: 10.1056/NEJMoa1209096, indexed in Pubmed: 23228172.
9. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol. 2014; 66(5): 815–825, doi: 10.1016/j.eururo.2014.02.056, indexed in Pubmed: 24647231.
10. Ryan C, Smith M, 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): 152–160, doi: 10.1016/s1470-2045(14)71205-7.
11. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018; 379(5): 417–427, doi: 10.1056/NEJMoa1803675, indexed in Pubmed: 29860937.
12. Hudes G, Carducci M, Tomczak P, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356(22): 2271–2281, doi: 10.1056/NEJMoa066838, indexed in Pubmed: 17538086.
13. Motzer RJ, Tannir NM, McDermott DF, et al. CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018; 378(14): 1277–1290, doi: 10.1056/NEJMoa1712126, indexed in Pubmed: 29562145.
14. https://clinicaltrials.gov/ct2/show/NCT02282020.
15. Kim TW, Elme A, Kusic Z, et al. A phase 3 trial evaluating panitumumab plus best supportive care vs best supportive care in chemorefractory wild-type KRAS or RAS metastatic colorectal cancer. Br J Cancer. 2016; 115(10): 1206–1214, doi: 10.1038/bjc.2016.309, indexed in Pubmed: 27736842.
16. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007; 25(13): 1658–1664, doi: 10.1200/JCO.2006.08.1620, indexed in Pubmed: 17470858.
17. Moore MJ, Goldstein D, Hamm J, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25(15): 1960–1966, doi: 10.1200/JCO.2006.07.9525, indexed in Pubmed: 17452677.
18. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012; 30(28): 3499–3506, doi: 10.1200/JCO.2012.42.8201, indexed in Pubmed: 22949147.
19. Joulain F, Proskorovsky I, Allegra C, et al. Mean overall survival gain with aflibercept plus FOLFIRI vs placebo plus FOLFIRI in patients with previously treated metastatic colorectal cancer. Br J Cancer. 2013; 109(7): 1735–1743, doi: 10.1038/bjc.2013.523, indexed in Pubmed: 24045663.
20. Chau I, Joulain F, Iqbal SU, et al. A VELOUR post hoc subset analysis: prognostic groups and treatment outcomes in patients with metastatic colorectal cancer treated with aflibercept and FOLFIRI. BMC Cancer. 2014; 14: 605, doi: 10.1186/1471-2407-14-605, indexed in Pubmed: 25142418.
21. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008; 26(12): 2013–2019, doi: 10.1200/JCO.2007.14.9930, indexed in Pubmed: 18421054.
22. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015; 26(8): 1547–1573, doi: 10.1093/annonc/mdv249, indexed in Pubmed: 26026162.
23. Del Paggio JC, Azariah B, Sullivan R, et al. Do Contemporary Randomized Controlled Trials Meet ESMO Thresholds for Meaningful Clinical Benefit? Ann Oncol. 2017; 28(1): 157–162, doi: 10.1093/annonc/mdw538, indexed in Pubmed: 27742650.

VIA MEDICA

REVIEW ARTICLE

Krzysztof Warzocha[1], Wojciech Homenda[2], Andrzej Pluta[3], Tomasz Sacha[3], Maria Cioch[4], Marek Dudziński[5], Dorota Krochmalczyk[6], Joanna Góra-Tybor[1], Ilona Seferyńska[1], Monika Joks[7], Marta Sobas[8]

[1]Department of Haematology, Institute of Haematology and Transfusion Medicine, Warszawa, Poland
[2]Department of Physiotherapy and Emergency Medicine, Pomeranian University, Słupsk, Poland
[3]Department of Haematology, *Collegium Medicum* of Jagiellonian University, Kraków, Poland
[4]Department of Haemato-oncology and Bone Marrow Transplantation, Medical University of Lublin, Poland
[5]Department of Haematology, Clinical Voivodeship Hospital no. 1, Rzeszów, Poland
[6]Clinical Ward of Haematology, University Hospital, Kraków, Poland
[7]Department of Haematology and Steam Cell Transplantation, University of Medical Sciences, Poznań, Poland
[8]Department of Haematology, Blood Neoplasm and Bone Marrows Transplantation, Medical University, Wrocław, Poland

Ruxolitinib in the treatment of patients with myelofibrosis — questions and answers

This is a translation of an article published in Polish in the journal „Hematologia" 2018, vol. 9, no. 4, 269–284. DOI: 10.5603/Hem.2018.0035

Introduction

Myelofibrosis (MF) is a clonal disease, arising as a result of somatic mutations in pluripotent stem cells. This leads to proliferation of atypical megakaryocytes and disfunction of the bone marrow microenvironment. Deregulation of JAK-STAT (Janus kinase — signal transducers and activators of transcription) pathway plays a key role in MF pathogenesis. Most patients carry mutation of the tyrosine kinase gene *JAK2* V617F in exon 14. In patients with wild-type *JAK2* gene, about 10% have mutation in the *MPL* W515L/K gene coding receptor for thrombopoietin, and in 80% of the remaining patients a mutation in the calreticulin gene (*CALR*) can be detected. All three described mutations lead to constitutive activation of JAK-STAT pathway, which results in increased secretion of proinflammatory cytokines, including interleukin 8, 10, 15, and tumour necrosis factor alpha (TNFα), as well as increased secretion of growth factors: vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and transforming growth factor beta (TGFβ). Excess of enumerated particles increases fibrosis, induces extra-medullary haematopoiesis, stimulates angiogenesis, and raises constitutional catabolism. Lack of either of these three mutations, found in about 10% of patients, is correlated with poor prognosis. Besides the presence of the described "driver" mutations, several types of mutations in genes regulating epigenetic changes can be found (including *ASXL1, EZH2, TET2, DNMT3A, IDH1/2, SRFS2, SRF3B1, TP53*). Detection of at least one mutation in *ASXL1, EZH2, SRSF2*, and *IDH1/2* genes determines high molecular risk (HMR), associated with shorter overall survival (OS) and higher risk of blastic transformation.

Described clinical and molecular features were incorporated in the newest prognostic scales, which supports optimal clinical management of patients with MF. In 2009, the International Working Group — Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) collaboration developed the International Prognostic Scoring System (IPSS) scale, based on five independent progression risk factors assessed at the time of MF diagnosis. This included: age over 65 years; presence of systematic symptoms; haemoglobin (Hb) concentration lower than 10 g/dl; hyperleukocytosis over 25 G/l; and the presence of at least 1% of blasts in peripheral blood smear. The IPSS scale was subsequently expanded into Dynamic IPSS (DIPSS), which included the possibility of acquisition of the aforementioned risk factors during the course of the disease, and provides prognostic stratification at any point of MF duration. In the DIPSS Plus scale, three additional independent prognostic factors were included: dependency on blood transfusions; unfavourable karyotype (trisomy 8;

Address for correspondence: prof. dr hab. n. med. Krzysztof Warzocha, Klinika Hematologii, Instytut Hematologii i Transfuzjologii, ul. Indiry Gandhi 14, 02–776 Warszawa, e-mail: warzocha@ihit.waw.pl

Translation: lek. Maciej Kawecki
Oncology in Clinical Practice, 2019, Vol. 15, No. 3, 167–179, DOI: 10.5603/OCP.2019.0021, Copyright © 2019 Via Medica, ISSN 2450–1654

monosomy 7/7q–; i(17q); inv(3); monosomy 5/5q– or 12p–; rearrangement of 11q23); and thrombocytopaenia (platelet count lower than 100 G/l).

Until recently, there was no drug to slow MF progression or to control systemic symptoms. Ruxolitinib — an inhibitor of JAK1/JAK2 kinase — is the first and, at present, only registered drug for MF that has changed this calamitous situation. It was approved by the Food and Drug Administration (FDA) in the USA in 2011 to treat patients with intermediate- or high-risk according to IPSS. In 2012, the European Medicines Agency (EMA) registered ruxolitinib in the EU to treat patients with MF, who had splenomegaly and/or systemic symptoms. Both decisions were based on the results of two phase III trials: COMFORT-I and COMFORT-II. The trials proved effectiveness of ruxolitinib in reducing splenic volume and in decreasing constitutive symptoms in MF patients with and without V617F mutation. Combined analysis of OS after three years of follow-up showed over 30% reduction in death risk in patients receiving ruxolitinib when compared to best available therapy or placebo. The described results and further statistical analyses led to the reimbursing ruxolitinib in Poland on 1st January 2017. Now the drug is available as a part of the Polish National Health Fund Drug Program, which includes patients with both primary and secondary MF, intermediate (2) or high IPSS risk, splenomegaly (spleen palpable ≥ 5 cm under ribs and/or splenomegaly present in ultrasound examination), and systemic symptoms.

Of utmost importance, ruxolitinib can be used in MF patients scheduled to receive allogenic haematopoietic stem cell transplantation (allo-HSCT). A decrease in concentration of proinflammatory cytokines, reduction of systematic symptom burden, shrinkage of spleen, and improvement of physical performance achieved before transplantation can lead to lower mortality and better outcomes associated with bone marrow transplant. According to European Leukaemia Net (ELN) and European Society for Blood and Marrow Transplantation (EBMT) guidelines, treatment with ruxolitinib should be initiated at least two months before a planned transplantation. The ruxolitinib dose should be gradually reduced 5–7 days before conditioning and withdrawn one day prior to the procedure. Retrospective analyses suggest that the presence of HMR mutations significantly reduce duration of response to ruxolitinib. Therefore, in patients with HMR mutations, who are qualified for bone marrow transplant, treatment with ruxolitinib should be restrained to the period before transplantation, without postponement of this potentially curative procedure.

However, ruxolitinib can lead to numerous adverse events, both haematological and non-haematological. Knowledge of the toxicity profile and proper adverse event management is required for effective and safe treatment. The article below presents the clinical aspects of ruxolitinib treatment in patients with MF, including groups with different clinical, laboratory, and pathological features. Expert opinions are supported with literature data and provide valuable advice for haematologists in their daily practice.

Ruxolitinib in patients with liver injury

The mean age of patients with MF is 65.9 years and with *polycythaemia vera* (PV) — 60.8 years [1]. This population is characterised by numerous comorbidities, including the presence of liver injury detected in physical examination, laboratory results, or in radiological imaging. With rising age, the rate of patients with hepatopathy increases, mostly due to toxic (alcohol, drugs) or metabolic (diabetes, hyperlipidaemias) factors. A significant proportion of hepatopathies arise from common infections with hepatitis B virus (HBV) or hepatitis C virus (HVC). Another significant factor responsible for hepatopathy in patients with myeloproliferative diseases is extra-medullar haematopoiesis, usually in the liver. As a result, hepatomegaly might be present in more than half of all patients with MF. One of the most common non-haematological adverse events observed with ruxolitinib in registration trials was an increase in aminotransferases activity. This might be observed in about 20–30% of treated patients. Additionally, ruxolitinib elimination might be prolonged in patients with liver insufficiency [2].

Evaluation of liver function is required before ruxolitinib treatment initiation. Laboratory studies should include aminotransferase activity and bilirubin concentration. Patients qualified for ruxolitinib treatment should have bilirubin concentration not higher than two-fold of the upper limit of normal (ULN) and alanine and aspartate aminotransferase activity lower than 2.5-fold of ULN. In patients with aminotransferases and/or bilirubin elevated below mentioned thresholds, detailed diagnostics should be undertaken. This is crucial because ruxolitinib treatment might lead to further increases in aminotransferase activity due to its hepatotoxic potential. Patients with elevated liver exams should be evaluated for the presence of active HBV or HCV hepatitis (HBsAg, anti-HBc, anti-HCV). Positive results should mitigate quantitative assessment for HBV-DNA and HCV-RNA. Infectious diseases specialist consultation might be required. Another possible cause of liver injury might be abuse of non-steroidal anti-inflammatory drugs. The most important task should be withdrawal of the over-used drugs. Liver regeneration may be supported with phospholipids (Esseliv forte, Essentiale forte, Essentialne Vital) or silymarin preparations (Sylimarol Vita). In patients with primary bone marrow fibrosis, who require numerous blood transfusions, secondary

haemochromatosis might be considered as a source of liver damage. Such patients should be monitored for ferritin concentration.

Patients with significant liver injury, defined as an increase in aminotransferase ≥ 2.5-fold ULN and increase in bilirubin concentration ≥ 2-fold ULN, require 50% reduction of ruxolitinib dose. The most important factor influencing initial ruxolitinib dose is the number of platelets (PLT). For example, for a patient with alanine aminotransferase increase of 1.5-fold over ULN and PLT number of 250 G/l, the initial treatment dose should be 10 mg of ruxolitinib administered twice daily. Monitoring with complete blood count, aminotransferase activity, and bilirubin concentration is required every 1–2 weeks for the first six weeks of treatment. If increased aminotransferase activity persist or if the PLT number decreases, the ruxolitinib dose should be again reduced.

Interactions of ruxolitinib with other drugs

Cytochrome P450 (CYP) inhibitors

Studies evaluating ruxolitinib *in vivo* showed that CYP3A4 is the main isoenzyme responsible for its metabolism. Patients treated with ruxolitinib may receive other drugs metabolised through the same enzymatic pathway. If ruxolitinib is administered simultaneously with strong CYP3A4 inhibitors or double CYP2C9 and CYP3A4 inhibitors (e.g. fluconazole), ruxolitinib dose should be reduced by 50% in two daily doses. Intensified monitoring of haematological parameters and regular physical examination screening for liver injury is advised. Strong CYP3A4 inhibitors include: boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

The ruxolitinib dose should not be reduced if the drug is given simultaneously with weak or moderate CYP3A4 inhibitors. These include ciprofloxacin, erythromycin, amprenavir, atazanavir, diltiazem, and cimetidine. However, patients should be closely monitored for potential cytopaenia when moderate CYP3A4 inhibitor treatment is initiated. Concomitant treatment with ruxolitinib and cytoreductive drugs or haematopoietic growth factors was not studied, and therefore the safety and efficiency of such treatment is unknown. Selective serotonin reuptake inhibitors (SSRI) increase serum ruxolitinib concentration because they inhibit activity of CYP3A4 isoenzymes. Such SSRIs include: fluoxetine, fluvoxamine, sertraline, and paroxetine. In patients receiving ruxolitinib, antidepressants with a mode of action different from SSRI are advised.

CYP3A4 inductors

Patients requiring chronic treatment with CYP3A4 inductors (such as avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin) should be closely monitored. Changes in CYP3A4 activity have limited impact on pharmacodynamics of ruxolitinib and is insignificant from a clinical standpoint. The dose of ruxolitinib can be gradually increased, considering the safety and effectiveness of treatment.

Infections

In retrospective analyses of patients with MF treated with ruxolitinib, about 20% develop infections, 90% of which are bacterial. Factors associated with infections are age over 65 years and concomitant treatment with corticosteroids.

Increased risk of infections with atypical strains of mycobacteria, pneumocystis, and reactivation of type B hepatitis should be noticed. Screening for human immunodeficiency virus (HIV), HBV, and HCV before ruxolitinib initiation is strongly encouraged. All patients with MF treated with ruxolitinib in clinical trials were offered annual influenza vaccination and pneumococcal vaccination because ruxolitinib treatment may result in immunodeficiency due to its potential to impair functioning of T cells, dendritic cells, and natural killer (NK) cells. For the same reason, patients treated with ruxolitinib must not receive live vaccinations. Fungal infections should be closely controlled because most antifungal drugs are CYP2C9 and CYP3A4 isoenzyme inhibitors and can lower therapeutic activity of ruxolitinib. Despite no pharmacological interaction between ruxolitinib and steroids, their concomitant usage is not recommended due to the unfavourable impact on cell-mediated immunity. Opportunistic infections, such as mycobacterial and pneumocystis infections, were described in patients treated with ruxolitinib and steroids. Similarly, despite no interaction between ruxolitinib and thalidomide described, both drugs have myelosuppressive potential and therefore patients receiving them simultaneously should be carefully monitored.

Ruxolitinib treatment in patients with anaemia. When to reduce the dose and when to withdraw therapy?

Anaemia is present in 35–54% of patients with MF at diagnosis and is considered an unfavourable prognostic factor [3]. With the course of the disease, the rate of anaemia rises and after a year is present in 47–64% of patients [3–6]. Ruxolitinib's mode of action, as well as the pathophysiological mechanism present in MF, result

in anaemia (with Hb concentration lower than 10 g/dl), being one of the most common adverse events. In both the COMFORT-I and COMFORT-II trials, patients receiving ruxolitinib experienced a decrease in Hb concentration during the first 12 weeks, with a nadir between the 8th and 12th week. Additionally, in both trials after 24 weeks of treatment, the Hb concentration increased to over 10 g/dl and stabilised at that level, which was independent of blood transfusions or ruxolitinib dose reductions [6–9]. Long-term observation from the COMFORT-I trial suggests that the incidence of new anaemia episodes grade 3 or 4 according to Common Terminology Criteria For Adverse Events (CTCAE) decreased with the length of treatment [10] and is not significantly higher than in patients receiving placebo [11]. These observations are confirmed by routine clinical practice. Anaemia is present in 70–75% of patients treated with ruxolitinib, usually during the first three months of treatment [12]. In most patients, the Hb concentration rises and stabilises thereafter. Analyses of data obtained in the COMFORT trials indicate that ruxolitinib-induced anaemia is not a negative prognostic factor and does not affect OS. For most experts who treat patients with MF, an Hb concentration decrease in the first weeks of ruxolitinib treatment is not an indication to reduce the dose or withdraw ruxolitinib, because this may lead to recurrence of symptoms present at the treatment initiation, usually within the first 10 days [12]. In patients without anaemia at the time of treatment initiation (e.g. with Hb concentration of 12 g/dl), who experienced decrease of Hb concentration to about 8.5 g/dl along with benefit from ruxolitinib, continuation of treatment with a possible dose reduction can be recommended. Nevertheless, most experts stress that the degree of anaemia is rarely the only reason for dose adjustment. In patients with anaemia and Hb concentration lower than 10 g/dl at the time of therapy initiation, the starting dose should be 10 mg twice daily. In patients dependent on blood transfusions, the recommended starting dose is 5 mg twice daily with a possible increase if tolerated. The initial three months of treatment are usually crucial to adjust doses for each patient [12].

A subgroup of patients do not achieve stabilisation of anaemia after the first three months of ruxolitinib treatment. Most experts agree that ruxolitinib dose reduction due to anaemia or blood transfusion dependency is not necessary, unless the decrease in Hb is substantial (e.g. from 11 g/dl to 6 g/dl) [12]. A mild decrease in Hb concentration (e.g. from 11 g/dl to 9 g/dl) is usually acceptable if the patient does not develop significant fatigue. In the case of Hb decrease from, as an example, 10 g/dl to less than 8 g/dl and concomitant significant fatigue, the decision about dose reduction should be preceded by consideration of whether symptoms associated with anaemia provide more burden than symptoms related to MF. The decision about dose reduction might be influenced by the patient's age. The treatment in younger patients might be more intensive than in patients older than 70 years, who require a more cautious approach. In patients who have low Hb concentration despite blood transfusions, along with a significant fatigue, and who prefer dose reduction despite adequate PLT number, dose reduction from the initial 20 mg twice daily to 15 mg or even 10 mg twice daily might be considered. The reduced dose should be continued with a close follow-up as long as the patient maintains response [12]. If an increase in Hb is observed, ruxolitinib dose escalation should be considered. If no change in Hb concentration is seen, erythropoiesis-stimulating agents (ESA) might be considered. In patients who develop rapid and significant decrease of Hb (to less than 6 g/dl) after prolonged treatment (e.g. 6–8 months) or who require blood transfusion more often than biweekly and who have recurrence of systemic symptoms and limited reduction of spleen volume, ruxolitinib withdrawal may be considered. The decision regarding dose reduction or ruxolitinib withdrawal should be taken individually, after discussion with the patient. Some patients might prefer continuation of treatment because it provides substantial reduction of MF symptoms, while others might prefer discontinuation to avoid frequent blood transfusions [12].

Erythropoietin in patients with myelofibrosis treated with ruxolitinib

Erythropoiesis-stimulating agents acts through the same pathway as endogenous erythropoietin, the concentration of which increases in patients treated with ruxolitinib as a result of *JAK2* pathway inhibition and suppression of proliferation and final differentiation of erythropoietic precursor cells. Therefore, it might be expected that ESA administration would provide limited benefit. However, it seems that for the increase in mean number of circulating erythrocytes the erythropoietin serum concentration is less important than its mean serum half-life time. Most currently used ESAs are characterised by a prolonged half-life when compared to endogenous erythropoietin and therefore may offer clinical benefit. ESA were used in 13 from 146 patients (9%) treated with ruxolitinib in COMFORT-II trial. Darbepoetin alpha was administered to three patients in doses 40–300 μg, 150–300 μg, and 500 μg; epoetin alpha was used in nine patients in doses between 10 and 40 thousand units; another erythropoietin preparation was administered to one patient at doses between 10 and 20 thousand units. Mean doses of ruxolitinib administered to patients receiving ESA and not receiving ESA were similar. Additionally, rates of patients requiring dose reductions were also similar. Due to the limited

number of this population, no statistical analyses comparing patients receiving and not receiving ESA were possible. Compared with lowest Hb concentration before ESA initiation, the lowest Hb concentration during first three months of ESA administration was increased in three patients, stable in seven patients, and lower in two patients. After three months of ESA treatment, Hb increase was observed in six patients (mean rise 7 g/dl) and Hb decrease in two patients (no data was reported regarding another five patients). In the analogic period, mean blood transfusion number decreased in two patients, was stable in one patient, and increased in three patients. Seven patients, who were independent of blood transfusion before ESA initiation, remained independent after three months of ESA treatment. Six weeks before ESA initiation grade 3 and 4 anaemia (according to CTCAE) was noticed in 10 among all 13 patients (77%). After six weeks of ESA treatment, in seven out of 13 patients (54%) anaemia grade decreased to grade 2 according to CTCAE. Among serious adverse events reported in eight patients receiving ESA, one episode of pulmonary embolism was judged to be ESA-related [3]. Results of other clinical trials indicate that ESA administration has limited effectiveness in MF patients who are blood transfusion dependent, have significant splenomegaly, have endogenous erythropoietin concentration of over 125 units/l, or have homozygotic mutation of *JAK2* gene [9]. No patient with normal endogenous erythropoietin concentration responded to ESA in another trial [11]. In a different trial undertaken in Mayo Clinic, no difference in response to ESA was seen regardless of initial erythropoietin concentration and was generally considered to be low (in 23% patients) [11]. Doubts regarding safety and possible association with leukaemic transformation have led to ESA being unrecommended in patients with MF, who are blood transfusion dependent or who have Hb concentration higher than 10 g/dl before treatment initiation [9, 11, 13]. The benefit seen in some patients receiving ESA in the COMFORT-II trial might be due to the prolonged ESA half-life compared to endogenous erythropoietin, and to the relatively short half-life of ruxolitinib. Obtained results suggest that in this group of patients ESA can be administered safely, without any negative impact on ruxolitinib effectiveness, and might be used to maintain ruxolitinib-related anaemia in the future.

Ruxolitinib in patients dependent on blood transfusions and with low PLT count

Anaemia and thrombocytopaenia are clinical manifestations of the advanced, fibrotic phase of myelofibrosis. The main mechanism leading to the development of these symptoms is suppression of erythropoietic and thrombopoietic precursors by progressive fibrosis in bone marrow and excessive degradation of erythrocytes and thrombocytes in an enlarged spleen. PLT count lower than 100 G/l, Hg concentration lower than 10 G/l, and blood transfusion dependency are poor prognostic factors and were included in IPSS, DIPSS, and DIPSS Plus classifications [14]. It is estimated that at the time of MF diagnosis anaemia with Hb concentration lower than 10 g/dl is present in 35–50% of patients and thrombocytopaenia with PLT count lower than 100 G/l is present in about 25% of patients [15]. Patients who begin treatment with ruxolitinib usually experience anaemia and thrombocytopaenia as a result of inhibition of JAK2 kinase-dependent erythropoiesis and thrombopoiesis. Both anaemia and thrombocytopaenia are strictly correlated with ruxolitinib dose. Patients with a tendency to develop thrombocytopaenia and anaemia should be carefully monitored. Avoiding significant decrease of platelet or erythrocyte count may limit the risk of serious adverse events, especially haemorrhages. Dose reduction is the most appropriate way of action in case of significant anaemia and/or thrombocytopaenia. Even temporary ruxolitinib withdrawal should be avoided because this may result in a flair-effect. Patients with severe decrease in Hb concentration and/or PLT count should receive packed red blood cells and/or platelet concentrate.

The first data regarding frequency of anaemia and thrombocytopaenia in patients treated with ruxolitinib came from the COMFORT-I and COMFORT-II trials. This evidence was the basis for recommendations regarding ruxolitinib dose reductions and interruptions. Because the first 8–12 weeks of treatment are associated with the highest risk of thrombocytopaenia, the initial ruxolitinib dose should be based on pre-treatment PLT count (PLT > 200 G/l — 2 × 20 mg, PLT 100 G/l to 200 G/l — 2 × 15 mg, PLT 50 G/l to 100 G/l — 2 × 5 mg). If the PLT count decreases below 50 G/l during ruxolitinib treatment, the dose should be slowly reduced and then, if necessary, ruxolitinib may be withdrawn [16–19]. Subsequent clinical trials (JUMP, EXPAND), which recruited patients with PLT count lower than in COMFORT trials, allowed the development of guidelines for ruxolitinib dose reductions in cases of more sever thrombocytopaenia. In American practice, ruxolitinib is withdrawn after the PLT count falls below 25 G/l, according to the Summary of Product Characteristics accepted by FDA. Because dose reduction might have a negative impact on treatment effectiveness, the highest tolerable dose should be reintroduced once the grade of toxicity allows [16].

The COMFORT trials showed that 61% of patients receiving ruxolitinib, who had normal pre-treatment haemoglobin concentration, developed anaemia, and

69% of patients with pre-treatment experienced anaemia worsening. Red blood cell parameters achieve their lowest point usually between eight and 12 weeks after treatment initiation and return to baseline after 24 weeks of therapy. In the case of anaemia, even with very low Hb concentration, ruxolitinib withdrawal is not recommended because the anaemia can be managed with blood transfusions and dose reductions, although this was not recommended in COMFORT trials. Exploratory analysis of the COMFORT trial data showed that, despite the fact that any degree of pre-treatment anaemia is a negative prognostic factor, anaemia associated with ruxolitinib treatment does not affect the patient's prognosis [15].

Maintenance of optimal ruxolitinib dose, adjusted to PLT count and Hb concentration, requires regular evaluation of complete blood count (CBC), especially during expected PLT and Hb nadir (between eight and 12 weeks after therapy initiation). Bi-weekly laboratory assessment can be recommended in all patients, even often in patients with low PLT count, who are dependent on blood transfusions. Adequate, regular laboratory evaluation and skilful dose maintenance might be crucial for successful ruxolitinib treatment [15].

IPSS and DIPSS — practice *versus* Drug Program. Which scale to use and how often to evaluate?

In 2009 the IWG-MRT group analysed a cohort of 1054 patients with newly developed MF and developed the IPSS scale. The analysis discriminated five independent progression risk factors: age over 65 years, presence of systemic symptoms, Hb concentration lower than 10 g/dl, hyperleukocytosis over 25 G/l, and the presence of at least 1% of blasts in a leukogram. Every factor was attributed one point. The number of points classifies patients to a group with low (0 points), intermediate-1 (1 point), intermediate-2 (2 points), or high risk (≥ 3 points), with median OS of, respectively, 135, 95, 48, and 27 months [20].

Expansion of IPSS, which was developed for patients before treatment initiation, led to the DIPSS scale, which incorporated acquisition of risk factors during the course of disease and can be used at any time. The DIPSS scale included the same parameters as the IPSS scale, with a 2-point value attributed to anaemia. The number of points classifies patients to groups with low (0 points), intermediate-1 (1–2 points), intermediate-2 (3–4 points), and high (5–6 points) risk, with median OS of, respectively: not reached, 168, 48, and 18 months [21]. The DIPSS scale can also assess risk of transformation to acute myeloid leukaemia: it can be estimated at, respectively, 0.3, 0.7, 2.6, and 8.6 cases per 100 patient-years [22].

In the newer DIPSS Plus scale an additional three independent prognostic factors were included: blood transfusions dependency, unfavourable karyotype (trisomy 8; monosomy 7/7q–; i(17q); inv(3); monosomy 5/5q– or 12p–; rearrangement of 11q23), and thrombocytopaenia (PLT count lower than 100 G/l) [23].

The Polish National Health Fund Drug Program requires attribution of potential patients to intermediate-2 or high-risk groups in the IPSS scale (which is based on the results of registration trials). If the patient was previously surveilled and attributed to the low-risk group, reassessment with the IPSS scale is discordant with its basic assumption of evaluation at the time of diagnosis. Patient surveillance should be undertaken with dynamic scales, such as DIPSS and DIPSS Plus. Unfortunately, during administrative controls the Drug Program is interpreted literally (not on the basis of merit), and therefore assessment with a scale other than IPSS during patient qualification can result in a financial fine for a controlled site. Prognostic scales should be actualised during each visit because any sign of progression might require treatment initiation or change. The Drug Program does not require further surveillance with the IPSS scale during treatment.

On a side note, it is worth mentioning that patients with MF, who are potential candidates for allo-HSCT, should not only be assessed with the aforementioned prognostic scales, but also undergo karyotype and molecular risk factor evaluation (including *CALR, JAK2, MPL,* and *ASXL1*). Patients with unfavourable karyotype and/or so-called "triple-negative" patients (without mutation in either *JAK2, CALR*, or *MPL*) with *ASXL1* mutation should be considered as candidates for allo-HSCT even with intermediate-1 risk prognosis in the DIPSS scale.

What, if any, antimicrobial prophylaxis should be administered during ruxolitinib treatment?

Treatment with ruxolitinib may result in immunosuppression, increasing the risk of infectious complications. The pathophysiological nature of this effect is complicated because ruxolitinib results in lower leukocyte count, including granulocytes, with concomitant impairment of lymphocyte T, dendritic cell, and NK cell functioning [24].

Grade 3 and 4 neutropaenia (according to CTCAE) was noted in 7.1% of patients treated with ruxolitinib and in 2% of patients treated with placebo in the COMFORT-I trial [10]. In the COMFORT-II trial, after five-year follow-up, grade 3 and 4 neutropaenia and leucopaenia was noted in 8.9% and 6.3% of patients, respectively (Tab. 1) [25].

Lussana et al. [26] review five phase III randomised clinical trials, six phase IV trials, and 28 case reports and

Table 1. Neutropaenia in patients included in the COMFORT trials (source [25])

	COMFORT-I		COMFORT-II	
	Ruxolitinib (n = 155)	Placebo (n = 151)	Ruxolitinib (n = 146)	BAT (n = 73)
Neutropaenia	19	4	NR	NR
Neutropaenia ≥ grade 3	7	2	NR	NR

BAT — best available therapy; NR — not reported

Table 2. Guidelines for antiviral prophylaxis during ruxolitinib therapy

Pathogen	Laboratory evaluation recommended before treatment initiation	Prophylaxis	Comments
CMV	IgG+, IgM–	Prophylaxis not recommended	CMV-PCR might be considered
EBV	IgG+, IgM–	Prophylaxis not recommended	EBV-PCR might be considered
VZV	IgG+, IgM–	Prophylaxis: acyclovir 2 × 400 mg/d.	
HSV	IgG+, IgM–	Prophylaxis: acyclovir 2 × 400 mg/d.	
HBV	HBsAg+	Prophylaxis: lamivudine 100 mg/d.	
HCV	HCV–, IgG+	No prophylaxis available	

CMV — cytomegalovirus; PCR — polymerase chain reaction; EBV — Epstein-Barr virus; VZV — varicella-zoster virus; HSV — herpes simplex virus; HBV — hepatitis B virus; HCV — hepatitis C virus

showed a statistically significant increase in the risk of shingles in patients treated with ruxolitinib. Data from the COMFORT-I and COMFORT-II trials showed that urinal tract infections grade 3 and 4 developed in 1% of patients, shingles in 4% of patients, tuberculosis in 1% of patients, and sepsis in 3% of patients. Combined analysis of clinical trials demonstrated that the most common infections were: shingles (8%), bronchitis (6%), and urinary tract infections (6%). The most common case reports described tuberculosis (n = 10), HBV reactivation (n = 5), and *Pneumocystis jirovecii* infections (n = 2). Less common cases of bilateral retinitis caused by *Toxoplasma gondii* and confirmed viral leukoencephalopathy were also reported [26].

Available data suggest that the increased infection risk during ruxolitinib treatment can have a clinically significant impact, but no recommended prophylaxis guidelines exist. A limited number of authors formulated practical tips that can be incorporated into clinical practice. Heine et al. [27] proposed undertaking laboratory evaluation aimed at detection of infectious agents before and during ruxolitinib treatment (Tab. 2).

Antibacterial prophylaxis is generally not recommended. Patients with tendencies towards urinary tract infections or bronchopneumonia with granulocyte count lower than 1 G/l may benefit from ciprofloxacin 500 mg administered twice daily until resolution of granulopaenia. Patients with positive results of *Quantiferon* test for *Mycobacterium tuberculosis* are advised to receive isoniazid 300mg daily. No prophylaxis for *Pneumocystis jirovecii* is recommended.

Because ruxolitinib treatment is not associated with an increased risk of fungal infection, no antifungal prophylaxis is recommended. It should be noted that many antifungal drugs are CYP enzyme inhibitors, and their administration might require ruxolitinib dose adjustment.

If ruxolitinib is used concomitantly with strong CYP-3A4 inhibitors or double CYP2C9 and CYP3A4 inhibitors, such as fluconazole, the ruxolitinib dose should be reduced by 50%. A fluconazole dose of 200 mg per day should not be exceeded. If simultaneous administration of ruxolitinib and CYP enzymes inhibitors is required, complete blood count should be evaluated more often — even 1–2 times per week.

Strong CYP3A4 inhibitors, such as clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole, also require a 50% reduction of the ruxolitinib dose. Mild and moderate CYP3A4 inhibitors, such as ciprofloxacin and erythromycin, do not require ruxolitinib dose modification, but close monitoring for cytopaenia should be undertaken.

Viral infections, significantly more common in patients receiving ruxolitinib, are a separate issue.

In some cases, antiviral prophylaxis with acyclovir might be considered (Tab. 2) [27].

Can the molecular profile of patient with myelofibrosis affect ruxolitinib effectiveness?

In both COMFORT trials, similar ruxolitinib effectiveness in reduction of splenic volume and control of systemic symptoms was seen in patients with and without V617F mutation [7, 28]. Additional analysis confirmed effectiveness of ruxolitinib in patients with *CALR* mutation [29]. Similar activity of ruxolitinib in both patient groups confirms that the main pathogenetic mechanism behind MF is overactivation of JAK–STAT pathway, which can independent of a specific single mutation.

Patients with MF often, despite the presence of driver-type mutation, have additional mutations in genes responsible for epigenetic modulation. This includes genes responsible for posttranslational modification of histones (*ASXL1*, frequency 10–35%; *EZH2*, frequency 7–10%), DNA methylation (*TET2, DNMT3A, IDH1/2*), mRNA splicing (*SRFS2, SRF3B1*), and DNA repair (*TP53*). The presence of at least one mutation in *ASXL1, EZH2, SRSF2*, or *IDH1/2*, called high-molecular risk (HMR,) is associated with shorter OS and higher risk of blastic transformation [30]. Guglielmelli et al. [31] analysed the impact of mutations on ruxolitinib effectiveness in 166 patients from the COMFORT-II trial. No impact of mutations was seen on treatment effectiveness (defined as reduction of splenomegaly and/or systemic symptoms) and on haematological toxicity profile (including anaemia and thrombocytopaenia). The beneficial effect of ruxolitinib on OS was independent of mutations associated with poor prognosis. After a median observation of 151 weeks, the predicted survival of patients treated with ruxolitinib in week 144 was 0.79 in the HMR group and 0.85 in the low-molecular risk (LMR) group, compared with, respectively, 0.58 and 0.71 in patients receiving the best available therapy (BAT). Patel et al. [32] assessed the impact of mutations on spleen volume reduction and on time to treatment discontinuation (TTD) in 95 patients treated with ruxolitinib in phase I/II trials. The authors of the analysis found a significant, negative impact of the presence of at least one HMR mutation on splenic response. Additionally, patients in the HMR group were characterised by a shorter TTD and OS. Spiegel et al. [33] evaluated correlation between mutations and similar parameters in a cohort of 100 patients with MF treated with ruxolitinib (77 patients) or momelotinib (23 patients). Unlike the observation of Patel et al. [32], this analysis showed no correlation between the presence of mutations and splenic response. However, it confirmed the negative impact of mutations on time to treatment failure (TTF) and OS.

The results of the presented analysis indicate that the presence of mutation from the HMR group significantly impairs duration of response to ruxolitinib. Therefore, in patients with mutation, who are potential candidates for allo-HSCT, treatment with ruxolitinib should not postpone the decision regarding transplantation, and should be considered only as a part of preparation to the procedure.

Ruxolitinib and risk of venous and arterial embolisms

Chronic myeloproliferative neoplasms (MPN) are characterised by an increased risk of venous and arterial embolisms. This affects 10–30% of patients before and 10–20% after MPN diagnosis [34]. Thromboembolic disease is most common in patients with PV and less common in patients with essential thrombocytopaenia (ET) and MF [35]. Risk factors associated with an increased risk of venous and arterial embolisms are: prior history of thromboembolic disease, presence of *JAK2* V617F mutation, and leukocytosis over 15 G/l [36]. Pathogenesis of MPN-related embolisms is mostly based on disfunction of red blood cells, white blood cells, platelets, and epithelial cells that raises adhesion of blood cells to endothelium [36, 37]. *In vivo* studies of JAK2+ neutrocytes showed increased creation of neutrophil extracellular traps (NET), which play a crucial role in disposal of pathogens, immunological reactions, and clot development [38]. Patients with PV have additional risk factors due to the presence of rheologic disturbances associated with increased haematocrit.

Association between ruxolitinib and thromboembolic diseases in patients with MF and PV was found in a metanalysis that included data from 750 patients participating in the COMFORT-I, COMFORT-II (patients with MF), and RESPONSE (patients with PV) trials [39]. The authors concluded that treatment with ruxolitinib was associated with lower risk of arterial and venous embolic disease when compared to treatment with placebo or BAT.

Research from Italy assessed the effectiveness and safety of ruxolitinib in patients with MPN (12 patients with MF, five with PV, and four with ET), who had history of portal vein thrombosis. No aggravation of portal vein thrombosis or worsening of oesophageal varices was seen during ruxolitinib treatment. One haemorrhagic adverse event was reported [40].

Effectiveness and safety of ruxolitinib treatment in patients with PV refractory or intolerant to hydroxycarbamide was assessed in the RESPONSE (222 patients) [41]

and RESPONSE-2 (149 patients) [42] trials. Ruxolitinib was more effective than BAT, with a significantly lower rate of thromboembolic disease in patients receiving ruxolitinib.

One phase II trial compared the effectiveness and safety of ruxolitinib with BAT in patients with ET refractory or intolerant to hydroxycarbamide [43]. No difference between ruxolitinib and BAT was seen in response rate. After two years of treatment, no difference in rates of thromboembolic and haemorrhagic events was observed. Another trial evaluated the effectiveness of ruxolitinib as a second-line treatment in 39 patients with ET [44]. Thromboembolic disease was seen in two patients and non-significant bleeding events in four patients.

Concluding, available data suggest that treatment with ruxolitinib results a in lower rate of embolic disease in patients with MF and PV, without a similar effect seen in patients with ET. No increase in haemorrhagic events is seen in MPN patients receiving ruxolitinib.

How to withdraw ruxolitinib? Principles of ending therapy

According to the Polish National Health Fund Drug Program, ruxolitinib treatment should be stopped if there is no spleen size reduction is seen after three months of treatment and/or if the spleen size reduction is less than 50% as assessed in USG after six months of treatment. Other mentioned situations are the development of new or a clear increase in previously present systemic symptoms, as well as unacceptable toxicity despite proper dose reduction and/or introduction according to the Summary of Product Characteristics. The last indications for ruxolitinib withdrawal are loss of gained response (assessed every six months) and transformation into acute leukaemia.

The most common adverse events seen with ruxolitinib — dose-dependent anaemia and thrombocytopaenia — developed in, respectively, 40.4% and 44.5% of patients in the COMFORT-II trial and rarely caused ruxolitinib withdrawal [45]. Other common toxicities include: leukopaenia, diarrhoea, bleeding, infections, thromboembolic events, arterial hypertension, and elevated liver enzymes. The decision about stopping ruxolitinib should include the notion that adverse events are most common in the first six months of treatment and usually decrease thereafter [46].

Long-term observations indicate that ruxolitinib needs to be stopped in 55% of patients after three-year follow-up (data from COMFORT-I and -II trials) [46]. Median OS after stopping ruxolitinib is 14 months [47].

Severe adverse reactions after ruxolitinib withdrawal, called ruxolitinib distress syndrome (RDS), are described in the literature. As confirmed in clinical trials, benefit from ruxolitinib was associated with a significant decrease in serum pro-inflammatory cytokines, such as IL-6, IL-1RA, TNFα, macrophage inhibitory protein 1b (MIP-1b), or C-reactive protein (CRP) [48]. Therefore, RDS might be caused by a rapid increase in previously low cytokine concentration. Ruxolitinib distress syndrome includes various clinical manifestations, from brisk reoccurrence of disease-related symptoms (including fast increase of spleen size and development of cytopaenia) to more severe conditions such as acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), spleen infarction, tumour lysis-like syndrome, or tumour septic shock-like syndrome.

Luckily, RDS is very rare, and only 10 cases have been described in the literature so far. Tefferi et al. [49] described RDS in five out of 47 patients who finished ruxolitinib treatment. Among them, three developed ARDS, from who two required mechanical ventilation and catecholamine infusion due to septic shock-like syndrome; one other patient developed DIC-like syndrome. In the COMFORT-I trial one patient experienced fever, acute respiratory failure, and splenic haemorrhage with infarction [7]. Other literature reports describe tumour lysis-like syndrome [50], ARDS [51], and recurring respiratory failure that resolved each time ruxolitinib was re-initiated [52]. RDS can be diagnosed only after exclusion of other possible causes and no clinical, laboratory or pathology finding can be called pathognomonic. Time to RDS occurrence varies from less than 24 hours to more than three weeks after ruxolitinib withdrawal [48].

According to the available literature, management of RDS should include not only supportive care, antibiotics, and mechanical ventilation if necessary, but also steroids or re-introduction of ruxolitinib, which can be switched to other JAK2 inhibitors after achieving RDS remission. Because RDS is very rare, no data enable formulation of ruxolitinib withdrawal guidelines. The authors of RDS case reports suggest close observation, slow dose decrease, and concomitant introduction of steroids [48, 49].

Management of ruxolitinib-associated hyperleukocytosis

Leukocytosis can be found in CBC of about 10–25% of patients with MF [53]. An increase in leukocyte count to over 25 G/l is a poor prognostic factor included in the IPSS, DIPSS, and DIPSS Plus scales [20, 21, 23]. In most patients, ruxolitinib has little to no effect on leukocyte count. In the COMFORT-I trial, mean pre-treatment leukocytosis was between 20 and 30 G/l and decreased to 15–20 G/l during treatment [54]. Only few cases of

grade 3 and 4 leukopaenia, according to World Health Organisation classification, developed. Some patients may experience an increase in leukocytosis or even hyperleukocytosis (leukocyte count of > 50–100 G/l). Every such case should be evaluated for the rate of peripheral myeloblasts, to exclude MF transformation into leukaemia.

A drug that might be used to decrease the leukocyte count is hydroxyurea (HU) — a cytostatic drug commonly used in patients with MF [55]. Until today, there are only a limited number of reports describing concomitant usage of ruxolitinib and HU in patients with MF [56, 57]. Caocci et al. [56] reported a case of a female patient in whom ruxolitinib treatment resulted in a leukocyte count increase up to 94 G/l and subsequent reoccurrence of systemic symptoms. After initiation of HU at a daily dose of 500 mg, the leukocyte count returned to normal and systemic symptoms vanished. In another patient with hyperleukocytosis, combined ruxolitinib and HU treatment resulted in normalisation of leukocyte count, a decrease in spleen size, improvement in systemic symptoms, and lower blood transfusion dependency [57]. It seems that for patients who receive ruxolitinib and develop a significant rise in leukocyte count, HU might be a safe and efficient therapeutic option.

Metabolic disorders in patients receiving ruxolitinib

Metabolic disorders, such as decrease in body weight, low serum cholesterol and albumin concentration, or cachexia, are a common problem in patients with MF, especially in more advanced cases [58–60]. If present, they significantly impair the patient's prognosis [20, 23, 58–60]. The aetiology of metabolic disorders is multifactorial [4, 22, 23, 61–66]. On the one hand, massive splenomegaly can lead to abdominal symptoms (pain, nausea, vomiting, early satiety) and decrease appetite [4, 66]. On the other hand, aberration in JAK–STAT pathway signalling can lead to overproduction of pro-inflammatory cytokines such as IL-6 or TNFα, which induce chronic inflammation, hypercatabolic state, loss of body weight, induction of cachexia, and reduction of liver albumin production [62–64].

According to the results of two clinical trials, the COMFORT-I study (ruxolitinib *vs.* placebo) and the COMFORT-II study (ruxolitinib *vs.* BAT), ruxolitinib can efficiently inhibit JAK1 and JAK2 kinases, leading to spleen volume reduction (probably due to reduction of extra-medullar haematopoiesis), a decrease in systemic symptoms and improvement of quality-of-life in patients with MF. Reduction of pro-inflammatory cytokine concentration, TNFα, IL-6, and CRP might also play role [4, 65].

A gradual increase in body weight of patients receiving ruxolitinib has been noticed in the COMFORT-I, COMFORT-II, and COMFORT-III trials [7, 64, 66]. This observation was confirmed in *post hoc* analysis of long-term (96 weeks) data from the COMFORT-I trial [61]. Among patients receiving ruxolitinib, 96.1% of patients achieved any body weight increase (mean 3.9 kg, as opposed to mean loss of 1.9 kg in patients receiving placebo; $p < 0{,}0001$) after 24 weeks of therapy, with comparable results after 36 weeks and even more profound gain of a mean 5.7 kg after 96 weeks. Body mass index (BMI) analysis showed a significant mean gain of 1.4 kg/m^2 after 24 weeks in the ruxolitinib arm (compared with a mean 0.7 kg/m^2 loss in the placebo arm; $p < 0.0001$), with comparable results after 36 weeks of treatment.

Additionally, the COMFORT-I trial also evaluated the concentration of leptin as a marker of adipose tissue. In patients receiving ruxolitinib, a more than two-fold increase in mean plasma leptin concentration was noted after four weeks of treatment and remained significant after 24 weeks. In patients receiving placebo a slight decrease in leptin concentration was noted during the same observation period [65].

In a *post hoc* analysis of the COMFORT-I trial, a rise in cholesterol concentration was noted in 96.8% of patients receiving ruxolitinib. After 24 weeks cholesterol increased 26.4% from baseline (29.5 mg/dl) in patients receiving ruxolitinib compared to a 3.3% fall (4.98 mg/dl) in patients receiving placebo. The cholesterol increase in the ruxolitinib group was maintained after 96 weeks of therapy (35.8% increase from baseline, 38 mg/dl). It should be emphasised that cholesterol concentration did not exceed 240 mg/dl of complete cholesterol and 160 mg/dl of low-density lipoprotein (LDL) cholesterol, thus not resulting in a higher risk of hypercholesterolaemia [61].

As with cholesterol, *post hoc* analysis of COMFORT-I data showed that 94.8% of patients receiving ruxolitinib experienced a rise in albumin concentration. The increase reached 5.8% (2.3 g/dl) at week 24 (compared to 1.7% [0.8 g/dl] decrease with placebo; $p < 0.0001$), with a stable results at week 10 and an additional rise of 7.6% (3.1 g/dl) at week 96 [61].

Both body mass increase and rise of cholesterol and albumin concentration was independent of the degree of spleen size reduction (≥ 35% *vs.* 10–35% *vs.* < 10%) and of the degree of systemic symptom reduction assessed with MyeloProliferative Neoplasm — Total Symptom Score (MPN-TSS) (not less than 50% *vs.* less than 50%) [61].

To sum up, ruxolitinib treatment, through inhibition of JAK1 and JAK2 kinases, leads to a decrease of pro-inflammatory cytokines concentration (IL-6 and TNFα). This results in reduction of chronic inflamma-

tion and systemic symptoms, suppression of hypercatabolism, and decrease in spleen size. Secondary to this, but no less important, is the observation that patients receiving ruxolitinib experience gradual and consistent (for over 96 weeks) improvement in body weight, cholesterol concentration (without increased risk of hypercholesterolaemia and cardio-vascular disorders), and albumin concentration. This effect might be partially responsible for the survival benefit associated with ruxolitinib in this patient population. Close follow-up of nutritional markers might provide valuable insights during ruxolitinib therapy.

Conclusions

The presented contemplations regarding clinical aspects of ruxolitinib treatment in patients with MF should provide answers to basic questions and doubts that may arise during therapy. The discussed issues concentrate mostly on management of patients with distinctive clinical and/or pathological profile and on dealing with certain adverse events. Crucial value can be attributed to proper monitoring of systemic symptoms, which are the best indicators of MF activity and can also overlap with possible adverse events.

The most important symptoms of MF are splenomegaly and cytokine-induced systemic symptoms that include weight loss, night sweats, fatigue, fever, and pruritus. Because the presence of systemic symptoms is required to qualify patients to the Polish National Health Fund Drug Program, and subsequent changes in symptoms provide insight into treatment effectiveness, objective symptom evaluation is crucial. This can be achieved with the MPN-TSS scale, which includes: fatigue; early satiety; discomfort in abdomen; decrease in activity and concentration; night sweats; pruritus; bone pains; fever; and unintentional weight loss.

Other important issue includes ruxolitinib distress syndrome, which can arise when ruxolitinib is withdrawn rapidly. Because this may lead to fierce and symptomatic cytokine storm, ruxolitinib withdrawal should be a gradual process. Nonetheless, stopping ruxolitinib may result in reoccurrence of systemic symptoms and an increase in spleen size. The decision regarding ruxolitinib withdrawal should be taken after careful deliberation and should be properly planned to limit the possibility of unexpected complications.

Patients with MF receiving ruxolitinib should be closely monitored to detect both haematological and non-haematological adverse events. The most common haematological adverse events are anaemia and thrombocytopaenia. In the COMFORT-I and COMFORT-II trials, all-grade anaemia according to CTCAE occurred in nearly all treated patients, with grade 3 and 4 events in 45.2% of patients in the COMFORT-I and 62% of patients in the COMFORT-II trial. Anaemia usually develops within the first eight weeks of treatment, with the nadir of Hb concentration between weeks 8 and 12, and then gradually increases and stabilises after six months of therapy. More than 50% of patients require blood transfusions, but ruxolitinib-related anaemia rarely requires dose modification or interruption. Other causes of anaemia should be ruled out, just as progression of MF itself.

All grade thrombocytopaenia, according to CTCAE, occurred in 70% of patients in the COMFORT-I and COMFORT-II trials. About 11% of patients experienced grade 3 and 4 thrombocytopaenia. Median time to thrombocytopaenia development was about eight weeks. Thrombocytopaenia was reversible after dose reduction or drug interruption, with a median time to PLT count recovery to over 50 G/l of two weeks. Decrease in PLT count might require ruxolitinib dose adjustment, mostly to avoid any treatment interruption that may limit therapy effectiveness. Patients with PLT count lower than 50 G/l should not be qualified for treatment with ruxolitinib. An additional indication for treatment interruption is neutropaenia greater than 0.5 G/l.

Regardless of PLT count, ruxolitinib treatment often results in haemorrhagic adverse events, most commonly subcutaneous haemorrhages, occurring in about 20% of patients. In the COMFORT-I and COMFORT-II trials, gastrointestinal bleeding of all grades occurred in 5% of patients and grade 3 and 4 events in 1.3% of patients. Intracranial bleeding developed in 1% of patients. Other bleeding events (including nosebleed, haematuria, or procedural bleedings) of all grade occurred in 13% of patients and of grade 3 and 4 in 2.3% of patients.

Non-haematological adverse events associated with ruxolitinib include headaches, dizziness (in about 15% of patients), diarrhoea, and mild to moderate increase in AlAt and AspAT activity (in about 20% of patients). Additionally, as a result of reduction of pro-inflammatory cytokine concentration, ruxolitinib exhibits immunosuppressive properties, including inhibition of dendritic cell activity, which leads to the suppression of CD4+ and CD8+ lymphocytes. Consequently, patients treated with ruxolitinib are more prone to infections, including opportunistic ones. Data from the COMFORT trials show increased risk of urinary tract infections and *Herpes zoster* infections in patients treated with ruxolitinib. Cases of HBV reactivation, tuberculosis, *Cryptococcus neoformans* pneumonia, toxoplasmosis uveitis, and progressive multifocal leukoencephalopathy were also reported. Therefore, screening for tuberculosis and hepatotropic viruses as part of routine pre-treatment evaluation should be considered. If positive, proper prophylaxis should be undertaken.

Ruxolitinib is excreted through kidneys and, to a lesser degree, through the digestive tract. Patients with severe renal impairment should receive reduced initial dose and patients with end-stage renal failure undergoing dialysis should receive a single daily dose after each dialysis. Patients with impaired liver function should receive 50% of the standard dose.

Because ruxolitinib interacts with numerous other agents, simultaneously used drugs should be revised and the ruxolitinib dose reduced if necessary. This is mostly due to the ruxolitinib metabolism, which involves mainly cytochrome CYP3A4 and partially CYP2C9. Fluconazole, a strong inhibitor of both mentioned cytochromes, increases ruxolitinib serum concentration by 100–300%. Therefore, the ruxolitinib dose should be reduced by 50%, with the same dosing schedule, if strong CYP3A4 inhibitors are administered (antifungal agents such as fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole; antiviral agents such as boceprevir, ritonavir, nelfinavir; and antibacterial agents such as clarithromycin).

Patients receiving ruxolitinib simultaneously with CYP3A4 inducers (such as carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort) should be carefully monitored and ruxolitinib dose increased according to achieved effectiveness and safety. No ruxolitinib dose adjustment is required when combined with mild and moderate CYP3A4 inducers (such as ciprofloxacin, erythromycin, diltiazem, cimetidine, atazanavir, and amprenavir).

References

1. Homenda W, Hellmann A. Epidemiologia przewlekłych zespołów nieloproliferacyjnych w województwie słupskim w latach 1994–1998. Acta Haematol Pol. 2003; 34(4): 419–431.
2. Chen X, Shi JG, Emm T, et al. Pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCB018424 phosphate) in renal and hepatic impairment patients. Clin Pharmacol Drug Dev. 2014; 3(1): 34–42, doi: 10.1002/cpdd.77, indexed in Pubmed: 27128228.
3. Guglielmelli P, Vannucchi AM. Struggling with myelofibrosis-associated anemia. Leuk Res. 2013; 37(11): 1429–1431, doi: 10.1016/j.leukres.2013.08.008, indexed in Pubmed: 24011697.
4. Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the mayo clinic experience. Mayo Clin Proc. 2012; 87(1): 25–33, doi: 10.1016/j.mayocp.2011.11.001, indexed in Pubmed: 22212965.
5. Harrison C, Mesa R, Ross D, et al. Practical management of patients with myelofibrosis receiving ruxolitinib. Expert Rev Hematol. 2013; 6(5): 511–523, doi: 10.1586/17474086.2013.827413, indexed in Pubmed: 24083419.
6. Levine RL, Gilliland DG. Myeloproliferative disorders. Blood. 2008; 112(6): 2190–2198, doi: 10.1182/blood-2008-03-077966, indexed in Pubmed: 18779404.
7. Verstovsek S, Mesa RA, Gotlib J, et al. COMFORT-I Investigators. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012; 366(9): 799–807, doi: 10.1056/NEJMoa1110557, indexed in Pubmed: 22375971.
8. Cervantes F, Vannucchi AM, Kiladjian JJ, et al. COMFORT-II Investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013; 122(25): 4047–4053, doi: 10.1182/blood-2013-02-485888, indexed in Pubmed: 24174625.
9. Cervantes F, Alvarez-Larrán A, Hernández-Boluda JC, et al. Darbepoetin-alpha for the anaemia of myelofibrosis with myeloid metaplasia. Br J Haematol. 2006; 134(2): 184–186, doi: 10.1111/j.1365-2141.2006.06142.x, indexed in Pubmed: 16740139.
10. Verstovsek S, Mesa RA, Gotlib J, et al. COMFORT-I Investigators. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica. 2015; 100(4): 479–488, doi: 10.3324/haematol.2014.115840, indexed in Pubmed: 25616577.
11. Huang J, Tefferi A. Erythropoiesis stimulating agents have limited therapeutic activity in transfusion-dependent patients with primary myelofibrosis regardless of serum erythropoietin level. Eur J Haematol. 2009; 83(2): 154–155, doi: 10.1111/j.16000609.2009.01266.x, indexed in Pubmed: 19366369.
12. Anemia can be a challenge but usually does not preclude successful treatment. http://www.researchtopractice.com/Myelofibrosis14/Commentary4 (29.08.2018).
13. Tsiara SN, Chaidos A, Bourantas LK, et al. Recombinant human erythropoietin for the treatment of anaemia in patients with chronic idiopathic myelofibrosis. Acta Haematol. 2007; 117(3): 156–161, doi: 10.1159/000097463, indexed in Pubmed: 17159338.
14. Cioch M, Jarosz P. Pierwotna mielofibroza — przegląd metod leczniczych. Acta Haematol Pol. 2014; 45(2): 143–148, doi: 10.1016/j.achaem.2014.04.001.
15. Gupta V, Harrison C, Hexner EO, et al. The impact of anemia on overall survival in patients with myelofibrosis treated with ruxolitinib in the COMFORT studies. Haematologica. 2016; 101(12): e482–e484, doi: 10.3324/haematol.2016.151449, indexed in Pubmed: 27587385.
16. Saeed I, McLornan D, Harrison CN. Managing side effects of JAK inhibitors for myelofibrosis in clinical practice. Expert Rev Hematol. 2017; 10(7): 617–625, doi: 10.1080/17474086.2017.1337507, indexed in Pubmed: 28571503.
17. Mesa RA, Komrokji RS, Verstovsek S. Ruxolitinib dose management as a key to long-term treatment success. Int J Hematol. 2016; 104(4): 420–429, doi: 10.1007/s12185-016-2084-1, indexed in Pubmed: 27567907.
18. Ikeda K, Ueda K, Sano T, et al. The amelioration of myelofibrosis with thrombocytopenia by a JAK1/2 inhibitor, ruxolitinib, in a post-polycythemia vera myelofibrosis patient with a JAK2 exon 12 mutation. Intern Med. 2017; 56(13): 1705–1710, doi: 10.2169/internalmedicine.56.7871, indexed in Pubmed: 28674362.
19. Al-Ali HK, Vannucchi AM. Managing patients with myelofibrosis and low platelet counts. Ann Hematol. 2017; 96(4): 537–548, doi: 10.1007/s00277-016-2697-8, indexed in Pubmed: 27209535.
20. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009; 113(13): 2895–2901, doi: 10.1182/blood-2008-07-170449, indexed in Pubmed: 18988864.
21. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010; 115(9): 1703–1708, doi: 10.1182/blood-2009-09-245837, indexed in Pubmed: 20008785.
22. Passamonti F, Cervantes F, Vannucchi AM, et al. Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. Blood. 2010; 116(15): 2857–2858, doi: 10.1182/blood-2010-06-293415, indexed in Pubmed: 20947690.
23. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011; 29(4): 392–397, doi: 10.1200/JCO.2010.32.2446, indexed in Pubmed: 21149668.
24. Manduzio P. Ruxolitinib in myelofibrosis: to be or not to be an immune disruptor. Ther Clin Risk Manag. 2017; 13: 169–177, doi: 10.2147/TCRM.S121683, indexed in Pubmed: 28243106.
25. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia. 2016; 30(8): 1701–1707, doi: 10.1038/leu.2016.148, indexed in Pubmed: 27211272.
26. Lussana F, Cattaneo M, Rambaldi A, et al. Ruxolitinib-associated infections: a systematic review and meta-analysis. Am J Hematol. 2018; 93(3): 339–347, doi: 10.1002/ajh.24976, indexed in Pubmed: 29150886.
27. Heine A, Brossart P, Wolf D. Ruxolitinib is a potent immunosuppressive compound: is it time for anti-infective prophylaxis? Blood. 2013; 122(23): 3843–3844, doi: 10.1182/blood-2013-10-531103, indexed in Pubmed: 24288410.

28. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012; 366(9): 787–798, doi: 10.1056/NEJMoa1110556, indexed in Pubmed: 22375970.
29. Guglielmelli P, Rotunno G, Bogani C, et al. COMFORT-II Investigators. Ruxolitinib is an effective treatment for CALR-positive patients with myelofibrosis. Br J Haematol. 2016; 173(6): 938–940, doi: 10.1111/bjh.13644, indexed in Pubmed: 26303809.
30. Guglielmelli P, Lasho TL, Rotunno G, et al. The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. Leukemia. 2014; 28(9): 1804–1810, doi: 10.1038/leu.2014.76, indexed in Pubmed: 24549259.
31. Guglielmelli P, Biamonte F, Rotunno G, et al. COMFORT-II Investigators, Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative (AGIMM) Investigators. Impact of mutational status on outcomes in myelofibrosis patients treated with ruxolitinib in the COMFORT-II study. Blood. 2014; 123(14): 2157–2160, doi: 10.1182/blood-2013-11-536557, indexed in Pubmed: 24458439.
32. Patel KP, Newberry KJ, Luthra R, et al. Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib. Blood. 2015; 126(6): 790–797, doi: 10.1182/blood-2015-03-633404, indexed in Pubmed: 26124496.
33. Spiegel JY, McNamara C, Kennedy JA, et al. Impact of genomic alterations on outcomes in myelofibrosis patients undergoing JAK1/2 inhibitor therapy. Blood Adv. 2017; 1(20): 1729–1738, doi: 10.1182/bloodadvances.2017009530, indexed in Pubmed: 29296819.
34. Sekhar M. Prevention and management of thrombosis in myeloproliferative neoplasms. Clin Adv Hematol Oncol. 2017; 15(3): 178–181.
35. Devendra KC, Falchi L, Verstovsek S. The underappreciated risk of thrombosis and bleeding in patients with myelofibrosis: a review. Ann Hematol. 2017; 96(10): 1595–1604, doi: 10.1007/s00277-017-3099-2, indexed in Pubmed: 28808761.
36. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood. 2013; 122(13): 2176–2184, doi: 10.1182/blood-2013-03-460154, indexed in Pubmed: 23823316.
37. Falanga A, Marchetti M. Thrombotic disease in the myeloproliferative neoplasms. Hematology Am Soc Hematol Educ Program. 2012; 2012: 571–581, doi: 10.1182/asheducation-2012.1.571.
38. Wolach O, Sellar RS, Martinod K, et al. Increased neutrophil extracellular trap formation promotes thrombosis in myeloproliferative neoplasms. Sci Transl Med. 2018; 10(436), doi: 10.1126/scitranslmed.aan8292, indexed in Pubmed: 29643232.
39. Samuelson BT, Vesely SK, Chai-Adisaksopha C, et al. The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis. Blood Coagul Fibrinolysis. 2016; 27(6): 648–652, doi: 10.1097/MBC.0000000000000446, indexed in Pubmed: 26569516.
40. Pieri L, Paoli C, Arena U, et al. Safety and efficacy of ruxolitinib in splanchnic vein thrombosis associated with myeloproliferative neoplasms. Am J Hematol. 2017; 92(2): 187–195, doi: 10.1002/ajh.24614, indexed in Pubmed: 27880982.
41. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015; 372(5): 426–435, doi: 10.1056/NEJM- oa1409002, indexed in Pubmed: 25629741.
42. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. Lancet Oncol. 2017; 18(1): 88–99, doi: 10.1016/S1470-2045(16)30558-7, indexed in Pubmed: 27916398.
43. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. Blood. 2017; 130(17): 1889–1897, doi: 10.1182/blood-2017-05-785790, indexed in Pubmed: 29074595.
44. Verstovsek S, Passamonti F, Rambaldi A, et al. Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: long-term phase 2 study results. Blood. 2017; 130(15): 1768–1771, doi: 10.1182/blood-2017-02-765032, indexed in Pubmed: 28827411.
45. Tefferi A. Primary myelofibrosis: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016; 91(12): 1262–1271, doi: 10.1002/ajh.24592, indexed in Pubmed: 27870387.
46. Mesa RA, Passamonti F. Individualizing care for patients with myeloproliferative neoplasms: integrating genetics, evolving therapies, and patient-specific disease burden. Am Soc Clin Oncol Educ Book. 2016; 35: e324–e335, doi: 10.1200/EDBK_159322, indexed in Pubmed: 27249739.
47. Newberry KJ, Patel K, Masarova L, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood. 2017; 130(9): 1125–1131, doi: 10.1182/blood-2017-05-783225, indexed in Pubmed: 28674026.
48. Coltro G, Mannelli F, Guglielmelli P, et al. A life-threatening ruxolitinib discontinuation syndrome. Am J Hematol. 2017; 92(8): 833–838, doi: 10.1002/ajh.24775, indexed in Pubmed: 28457008.
49. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc. 2011; 86(12): 1188–1191, doi: 10.4065/mcp.2011.0518, indexed in Pubmed: 22034658.
50. Dai T, Friedman EW, Barta SK. Ruxolitinib withdrawal syndrome leading to tumor lysis. J Clin Oncol. 2013; 31(29): e430–e432, doi: 10.1200/JCO.2012.47.6473, indexed in Pubmed: 23752116.
51. Beauverd Y, Samii K. Acute respiratory distress syndrome in a patient with primary myelofibrosis after ruxolitinib treatment discontinuation. Int J Hematol. 2014; 100(5): 498–501, doi: 10.1007/s12185-014-1628-5, indexed in Pubmed: 25034748.
52. Herman DD, Kempe CB, Thomson CC, et al. Recurrent hypoxemic respiratory failure. Beyond the usual suspects. Ann Am Thorac Soc. 2014; 11(7): 1145–1148, doi: 10.1513/AnnalsATS.201403-127CC, indexed in Pubmed: 25237993.
53. Tefferi A, Wassie EA, Lasho TL, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia. 2014; 28(7): 1472–1477, doi: 10.1038/leu.2014.3, indexed in Pubmed: 24402162.
54. Verstovsek S, Mesa RA, Gotlib J, et al. COMFORT-I Investigators. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017; 10(1): 55, doi: 10.1186/s13045-017-0417-z, indexed in Pubmed: 28228106.
55. Kuykendall AT, Talati C, Al Ali N, et al. The treatment landscape of myelofibrosis before and after ruxolitinib approval. Clin Lymphoma Myeloma Leuk. 2017; 17(12): e45–e53, doi: 10.1016/j. clml.2017.08.002, indexed in Pubmed: 28869184.
56. Caocci G, Ghiani S, Mocci C, et al. Combination therapy with ruxolitinib and hydroxyurea for the treatment of myeloid-predominant leukocytosis in a patient with myelofibrosis. Acta Haematol. 2018; 139(3): 164–165, doi: 10.1159/000487582, indexed in Pubmed: 29597187.
57. Cerchione C, Peluso I, Nappi D, et al. Ruxolitinib rechallenge in combination with hydroxyurea is effective in reverting cachexia and reducing blood transfusion demand and splenomegaly symptoms in a patient with primary myelofibrosis. Ann Hematol. 2017; 96(4): 697–699, doi: 10.1007/s00277-017-2938-5, indexed in Pubmed: 28197723.
58. Mesa RA, Schwager S, Huang J, et al. Weight loss, splenomegaly, and hypocholesterolemia in myeloproliferative neoplasms: patterns and relevance from the pre JAK2 inhibitor era [abstract]. Blood. 2009; 114(22): 3918.
59. Mesa RA, Huang J, Schwager S, et al. Hypocholesterolemia is independently associated with decreased survival in patients with primary myelofibrosis: an analysis of lipid profiles in 558 myeloproliferative patients [abstract]. Blood. 2007; 110(11): 2548.
60. Sulai N, Mengistu B, Gangat N, et al. Decreased levels of total or HDL cholesterol in primary myelofibrosis are associated with shortened survival: DIPSS-Plus independent prognostic value [abstract]. Blood. 2012; 120(21): 2851.
61. Mesa RA, Verstovsek S, Gupta V, et al. Effects of ruxolitinib treatment on metabolic and nutritional parameters in patients with myelofibrosis from COMFORT-I. Clin Lymphoma Myeloma Leuk. 2015; 15(4): 214–221.e1, doi: 10.1016/j.clml.2014.12.008, indexed in Pubmed: 25682576.
62. Argiles JM, Lopez-Soriano FJ, Busquets S. Counteracting inflammation: a promising therapy in cachexia. Crit Rev Oncog. 2012; 17(3): 253–262, doi: 10.1615/critrevoncog.v17.i3.30, indexed in Pubmed: 22831156.
63. Fearon KCH, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012; 16(2): 153–166, doi: 10.1016/j.cmet.2012.06.011, indexed in Pubmed: 22795476.
64. Tefferi A, Vaidya R, Caramazza D, et al. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. J Clin Oncol. 2011; 29(10): 1356–1363, doi: 10.1200/JCO.2010.32.9490, indexed in Pubmed: 21300928.
65. Verstovsek S, Mesa RA, Gotlib J, et al. COMFORT-I Investigators, COMFORT Investigators, COMFORT-I investigators. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med. 2010; 363(12): 1117–1127, doi: 10.1056/NEJMoa1002028, indexed in Pubmed: 20843246.
66. Tefferi A. JAK inhibitors for myeloproliferative neoplasms: clarifying facts from myths. Blood. 2012; 119(12): 2721–2730, doi: 10.1182/blood-2011-11-395228, indexed in Pubmed: 22279053.

VIA MEDICA

CASE REPORT

Rafał Maksim[1], Ewa Sierko[1, 2], Dominika Hempel[1, 2], Justyna Burzyńska-Śliwowska[3], Kamila Kidrycka[3], Piotr Szumowski[4], Krystian Kidrycki[5], Marek Z. Wojtukiewicz[2], Tomasz Filipowski[1], Małgorzata Mojsak[4]

[1]Department of Radiotherapy, Comprehensive Cancer Centre, Bialystok, Poland
[2]Department of Oncology, Medical University of Bialystok, Poland
[3]Department of Radiology, Comprehensive Cancer Centre, Bialystok, Poland
[4]Department of Gastroenterology and Internal Medicine, Medical University of Bialystok, Poland
[5]Bialystok Science and Technology Park within the Laboratory of Molecular Imaging and Technology Development at the Medical University of Bialystok, Poland

The usefulness of an ^{18}F-FDG-PET/MR examination in a patient with rectal and breast cancer. A case report

Address for correspondence:
Dr hab. n. med. Ewa Sierko
Zakład Radioterapii
Białostockie Centrum Onkologii
ul. Ogrodowa 12, 15–027 Białystok
Phone: +48 602 337 020
e-mail: ewa.sierko@iq.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 3, 180–184
DOI: 10.5603/OCP.2019.0015
Translation: dr Elżbieta Stelmaszczyk

ISSN 2450–1654

ABSTRACT

Recently, we have gained access to innovative radiological and metabolic examination methods. One of these methods is PET/MRI with fluorodeoxyglucose (18F-FDG) tracer. Performing this innovative examination in a 69-year-old woman with diagnosed rectal cancer brought additional benefits. The use of PET/MRI resulted in precise clinical staging, the detection of a synchronous early-stage right breast cancer, and in the optimisation of treatment of both cancers. To date, diagnostic guidelines concerning rectal and breast cancers do not recommend the use of functional imaging for routine imaging.

Key words: PET/MR, rectal cancer, breast cancer

Oncol Clin Pract 2019; 15, 3: 180–184

Introduction

New imaging methods make diagnostics more precise and help us diagnose illnesses at an earlier stage, which in turn increases the chances of curing the patient. One of the innovative diagnostic tools is a hybrid technique — MRI combined with PET. One of the main advantages of this technology is its ability to morphologically image the whole body while also imaging its metabolism by means of PET with the fluorodeoxyglucose isotope ^{18}F. It is worth noting that the classic PET/CT method uses a diagnostically sub-optimal low-dose cone beam tomography, whereas in PET/MRI the magnetic resonance images are of high quality, with T1 sequences with and without contrast, T2, and diffusion weighted imaging.

Case report

A 69-year-old patient in good general condition WHO-0, was referred to the Oncology Centre of Bialystok due to rectal cancer. A tumour was found during ordinary colonoscopy. The histopathological material obtained during the examination showed an intestinal type of adenocarcinoma. The patient had smoked about 10 cigarettes per day for 20 years and suffered from hypertension. She had a family record of breast cancer with her sister. The patient reported no problems. In the clinical examination the rectal tumour was beyond reach during rectal exam. CT showed a rectal tumour located about 3 cm behind the anal sphincter, infiltrating the mesorectum and possibly metastatic regional lymph nodes. About 12 cm

from the sphincter colonoscopy visualised a stiff, exophytic infiltration, bleeding on contact, narrowing the lumen to an extent that prevented further insertion of the apparatus. The patient was then preliminarily qualified for neoadjuvant radiochemotherapy with delayed surgery time.

The patient also underwent a PET/MRI examination, using a 3T Biograph mMR Siemens® device with ^{18}F-FDG tracer. The examination showed irregular thickening of the rectal wall to 14 mm over 72 mm, starting at about 50 mm above anal sphincter, with increased FDG uptake at SUV_{max} = 15.9. The fat planes around the visualised tumour were effaced but no infiltration to surrounding organs was found. The local lymph nodes: pararectal, parasigmoid, and presacral did not exceed 7 mm in diameter in the MRI examination, and no increased FDG uptake was found in PET. Moreover, T2- and T1-weighted images showed a somewhat well-limited focal lesion sized 20 × 18 mm of spicular outline with slightly increased FDG uptake — SUV_{max} = 2.2 in the right breast, in the lower internal quadrant, and a swollen lymph node under the right arm, sized 11 × 7 mm with a slightly increased FDG uptake at SUV_{max} = 0.78. Clinical examination showed no breast tumour nor any swollen axillary lymph nodes. The patient, due to her earlier family history, avoided screening tests for breast cancer.

Following further assessment of the clinical stage of the disease (which included the results of PET/MRI examination) it was decided that a new form of therapy should be adopted. The patient underwent 3D radiotherapy of X15 MV for the rectal tumour, mesorectum, and regional lymph nodes up to a total dose of 25 Gy in five fractions, then she underwent a surgical frontal rectal resection. During her stay at the Oncological Surgery Department, the patient underwent a core needle biopsy of the suspicious right breast tumour, which was visualised in PET/MRI, in order to collect diagnostic material for histopathological examination.

The postoperative histopathological examination from the rectum showed an ulcerated tumour taking up nearly the entire perimeter of the intestinal wall over a 4-cm segment. The transverse cross-section showed a whitish infiltration, which macroscopically included the subcutaneous tissue surrounding the rectum. Morphologically, a G2 adenocarcinoma with a mucous component — ypT3 — was diagnosed. All (15) lymph nodes of the mesorectum were inflamed. In the material obtained during the core-needle biopsy of the right breast, invasive duct carcinoma with a malignancy level at G2 was characterised by oestrogen receptor expression in 97% of the cancer cells, progesterone receptor expression in less than 1% of the cells, lack of HER2 expression, and the presence of Ki-67 protein

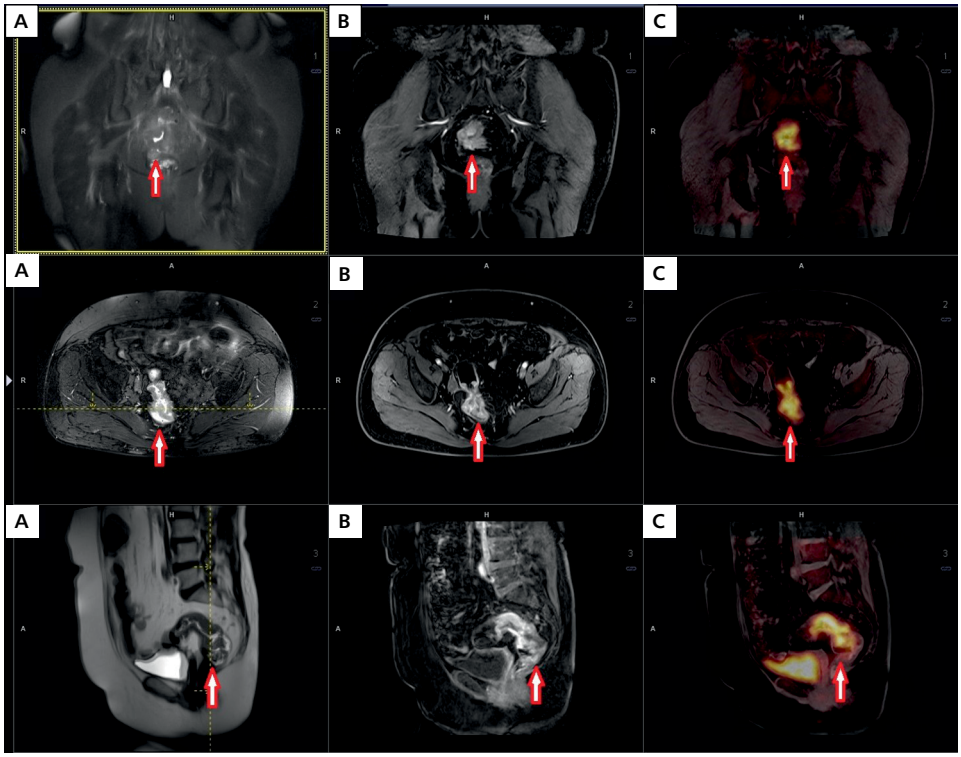

Figure 1. PET/MRI scan using a 3T Biograph mMR Siemens® with ^{18}F-FDG. The images show rectal carcinoma (arrow), respectively: **A.** MRI in T2-weighted sequence; **B.** MRI in T1-weighted sequence; and **C.** the fusion of MRI images in T1-weighted sequence and PET

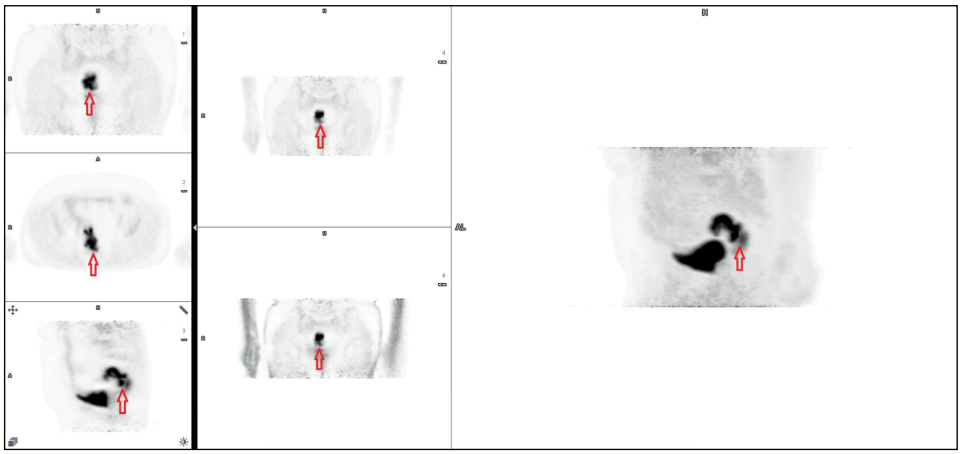

Figure 2. PET scan with tracer ^{18}F-FDG — metabolic imaging of the rectal carcinoma. The arrow points to the area of increased FDG uptake in the tumour, SUV — 15.9

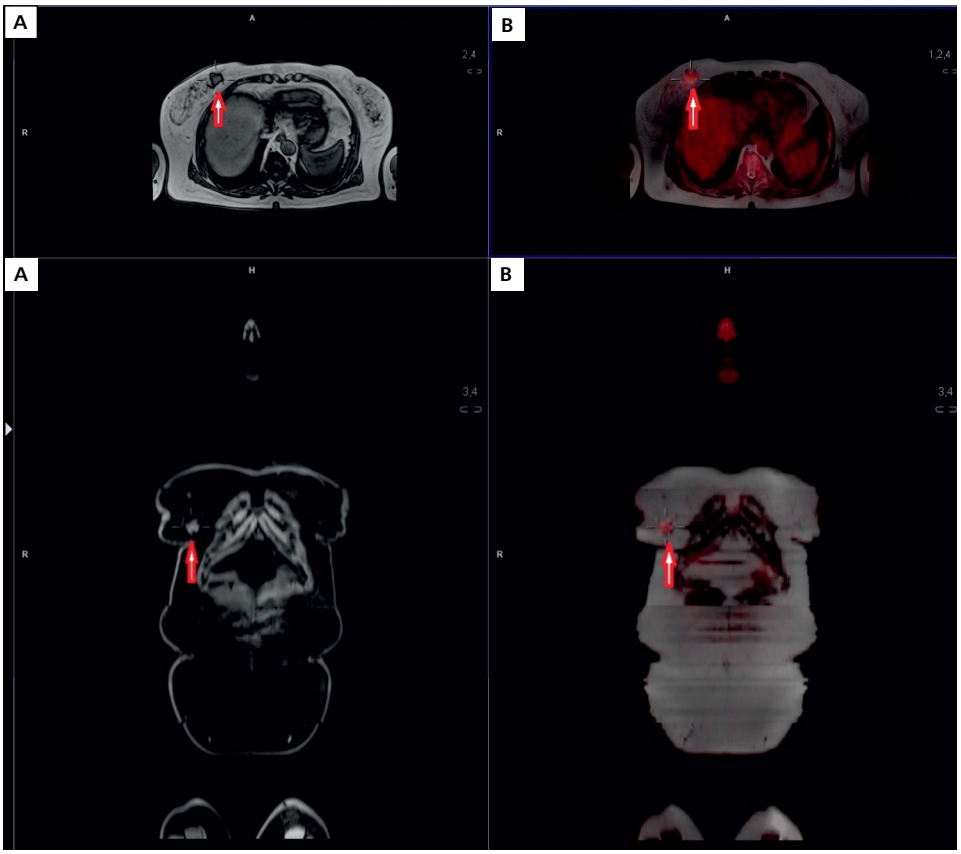

Figure 3. PET/MRI scan using a 3T Biograph mMR Siemens® with ^{18}F-FDG. The images show breast cancer (the arrow), respectively: **A.** MRI in T1-weighted sequence; **B.** the fusion of MRI images in T2-weighted sequence and PET

in 45% of the cells. In the material obtained during a USG-guided fine-needle biopsy of the right axillary lymph node visualised in PET/MRI, cells suspected of malignancy were found. The patient underwent a breast-conserving surgery and sentinel lymph node (SLN) procedure. Pathological postoperative breast material showed a white irregular tumour, with uneven boundaries, sized: 2.3 × 2 cm. Microscopically the image corresponded to invasive G2, pT2 carcinoma. In one of the seven sampled axillary lymph nodes a macrometastasis of the breast cancer was found. Next, the patient received adjuvant chemotherapy based on epirubicin and cyclophosphamide (four courses), then radical 3D radiotherapy X6/15 MV for the right breast and right

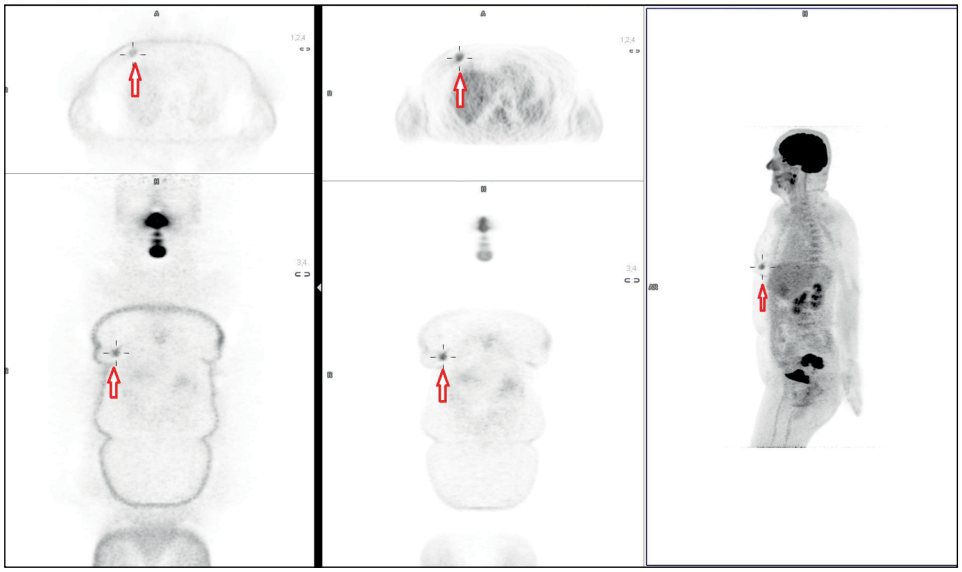

Figure 4. PET scan using a 3T Biograph mMR Siemens® with ^{18}F-FDG — metabolic imaging of the breast cancer. The arrow points to an area of increased FDG uptake in the tumour, SUV — 2.2

axillary lymph nodes up to the total dose of 45 Gy administered in 20 fractions. The dose was increased to the postoperative site after the excised breast tumour at 16 Gy in eight fractions. Radiotherapy was completed in March 2018. The patient is now undergoing hormonal therapy with letrozole.

Discussion

MRI examination has been used for many years now in preoperative evaluation of rectal carcinoma progression [1]. MRI makes it possible to better assess the risk of infiltration of the circular surgical margin, to better match and optimise therapies, and to single out the group of patients who do not need preoperative treatment [2]. The guidelines of the Polish Society of Clinical Oncology regarding evaluation of the local stage of rectal carcinoma suggest MRI examination of the lesser pelvis and transrectal USG [2]. Additionally, it is recommended that the thoracic cavity, abdominal cavity, and the pelvis [2] be CT scanned. In patients with rectal cancer, PET scan is not recommended routinely in the diagnostic process but only when a local relapse is suspected [2]. In the National Comprehensive Cancer network (NCCN) guidelines, a pelvic MRI with contrast is mandatory unless there are contraindications for the examination, e.g. an implanted heart pacer. PET/CT is recommended only in patients with confirmed disease spread with potentially resectable metastases [3]. Scientific publications do not report any significant information on the use of PET in the primary evaluation of rectal cancer; however, there is a lot of research confirming the effectiveness of PET at verifying the presence of metas-

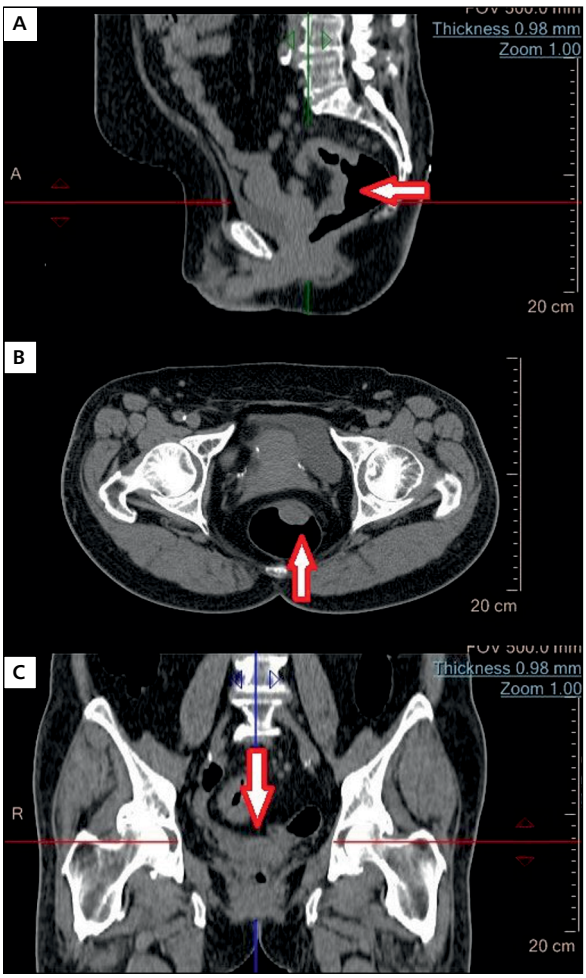

Figure 5. CT localising examination, no contrast. The images show rectal carcinoma (the arrow) in: **A.** the sagittal plane; **B.** the transverse plane; and C. the frontal plane

tases in regional lymph nodes (sensitivity and specificity are, respectively, 56.8% and 90.3%) [4], or at confirming the spread of cancer (sensitivity and specificity respectively — 91% and 76%) [5]. Similarly, PET examination is not a standard tool in breast cancer diagnostics; however, research suggests that it is very sensitive and specific in diagnosing this type of cancer — respectively, 97% and 80% [6], for lymph nodes — 46.3% and 91.1% and distant metastases of this cancer — 86–100% and 90–98% [7]. MRI with contrast is used in breast diagnostic procedures more often. In a large group of women (n = 2995) with intermediate and high risk of breast cancer, using this method resulted in finding just 27 new cases of cancer. However, it was characterised by a better sensitivity than ultrasonography (USG) or mammography (their sensitivity was, respectively: 86%, 58%, and 57%) [8]. In the presented case, the results of colonoscopy, CT, and PET/MRI were different with respect to the distance of the rectal tumour from the anal sphincter. The distance was respectively 12 cm, 3 cm, and 5 cm. The literature reports differences of this sort between MRI and colonoscopy [9]. They can amount to –3 to +8 cm [9]. It is likely to be caused by the lack of agreement between endoscopists regarding the proper technique of measuring the distance between the rectal tumour and the sphincter [9]. Jacobs at al. emphasise that in order to assess the distance between the rectal tumour and the sphincter an MRI examination should be performed [9]. Proper evaluation of the stage of the disease and the location of the rectal tumour in respect to the anal sphincter is crucial for the possibility of surgical intervention that could spare that sphincter, thus preserving of the continuity of digestive tract and consequently the quality of life of the patient after the treatment is finished [10]. Owing to precise, effective MRI imaging in PET/MRI in the reported case, it was possible to pinpoint with better precision the depth of the intestinal wall infiltration by the rectal carcinoma. The PET examination itself helped the patient to evaluate the surrounding lymph nodes, which initially looked suspicious in CT images. Re-evaluation of the stage of the disease using PET/MRI changed the therapeutic regiment from the so-called "long" chemotherapy to a short, five-day radiotherapy only. The results obtained in PET/MRI were confirmed in pathological examination in the case of the stage of both the rectal cancer (pT3N0) and the breast cancer (pT2N1). Performing a PET/MRI scan of the reported patient's body made it possible to detect breast cancer and to effectively treat both cancers. There are reports that in women with a family history of breast cancer with *BRCA* mutation and without it, using MRI leads to earlier detection of intraductal and invasive family or heritable breast cancer [11]. PET examination in women from a high-risk group of developing breast cancer offers better prospects of evaluating the stage of the disease for as many as 34.8% of patients and, consequently, it can help change therapeutic decisions in 74.1% of cases [12].

Conclusions

Simultaneous application of PET/MRI methods facilitates decreasing the time of diagnostics and helps optimise the treatment plan. More research is necessary to identify the group of patients who will gain clear therapeutic benefits from MRI imaging combined with PET.

References

1. Battersby N, How P, Moran B, et al. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model. Annals of Surgery. 2016; 263(4): 751–760, doi: 10.1097/sla.0000000000001193.
2. Bujko K, Herman R, Pałucki J et al. Rak odbytnicy, aktualizacja na dzień 02.12.2015. In: Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych. Tom I. Krzakowski M, Warzocha K et al. (ed.). Via Medica, Gdańsk 2013; 199.
3. NCCN Clinical Practice Guidelines in Oncology, Rectal Cancer, Version 3.2018.
4. Sasaki K, Kawasaki H, Sato M, et al. Impact of Fluorine-18 2-Fluoro-2-Deoxy-D-Glucose Uptake on Preoperative Positron Emission Tomography/Computed Tomography in the Lymph Nodes of Patients with Primary Colorectal Cancer. Dig Surg. 2017; 34(1): 60–67, doi: 10.1159/000448222, indexed in Pubmed: 27454870.
5. Brush J, Boyd K, Chappell F, et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. Health Technol Assess. 2011; 15(35): 1–192, iii, doi: 10.3310/hta15350, indexed in Pubmed: 21958472.
6. Magometschnigg HF, Baltzer PA, Fueger B, et al. Diagnostic accuracy of (18)F-FDG PET/CT compared with that of contrast-enhanced MRI of the breast at 3 T. Eur J Nucl Med Mol Imaging. 2015; 42(11): 1656–1665, doi: 10.1007/s00259-015-3099-1, indexed in Pubmed: 26121928.
7. Vercher-Conejero JL, Pelegrí-Martinez L, Lopez-Aznar D, et al. Positron emission tomography in breast cancer. Diagnostics (Basel). 2015; 5(1): 61–83, doi: 10.3390/diagnostics5010061, indexed in Pubmed: 26854143.
8. Huzarski T, Górecka-Szyld B, Huzarska J, et al. Polish Hereditary Breast Cancer Study Group. Screening with magnetic resonance imaging, mammography and ultrasound in women at average and intermediate risk of breast cancer. Hered Cancer Clin Pract. 2017; 15: 4, doi: 10.1186/s13053-017-0064-y, indexed in Pubmed: 28265306.
9. Jacobs L, Meek DB, van Heukelom J, et al. Comparison of MRI and colonoscopy in determining tumor height in rectal cancer. United European Gastroenterol J. 2018; 6(1): 131–137, doi: 10.1177/2050640617707090, indexed in Pubmed: 29435323.
10. Dimitriou N, Michail O, Moris D, et al. Low rectal cancer: Sphincter preserving techniques-selection of patients, techniques and outcomes. World J Gastrointest Oncol. 2015; 7(7): 55–70, doi: 10.4251/wjgo.v7.i7.55, indexed in Pubmed: 26191350.
11. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol. 2005; 23(33): 8469–8476, doi: 10.1200/JCO.2004.00.4960, indexed in Pubmed: 16293877.
12. Kowalski ES, Cohen JD, Snider JW, et al. Positron emission tomography/computed tomography (PET/CT) in the initial evaluation of women with nonmetastatic breast cancer can frequently alter management. Int J Radiat Oncol Biol Phys. 2017; 99(2): E25–E26, doi: 10.1016/j.ijrobp.2017.06.652.

VIA MEDICA

CASE REPORT

Aleksandra Piórek, Adam Płużański, Maciej Krzakowski

Department of Lung and Thoracic Cancers, Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland

Advanced solitary fibrous tumour of the pleura — a case report and literature review

Address for correspondence:
Lek. Aleksandra Piórek
Klinika Nowotworów Płuca i Klatki Piersiowej, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie w Warszawie
e-mail: opiorek@tlen.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 3, 185–189
DOI: 10.5603/OCP.2019.0017
Translation: dr Elżbieta Stelmaszczyk

ISSN 2450–1654

ABSTRACT

The solitary fibrous tumour (SFT) is a rare tumour, which usually occurs in the pleura. Patients with an advanced SFT have a poor prognosis. The treatment options for recurrent disease are especially limited. We present the case of a 55-year-old female patient with a malignant SFT of the pleura, who received conventional chemotherapy and targeted therapy. This paper focuses on systemic therapy in the treatment of metastatic SFT.

Key words: solitary fibrous tumour, pleura, chemotherapy

Oncol Clin Pract 2019; 15, 3: 185–189

Introduction

The solitary fibrous tumour (SFT) is a mesenchymal tumour, which in most cases concerns the pleura [1]. These tumours constitute less than 5% of pleural tumours and less than 2% of all soft tissue tumours [1]. SFT occurs in men and women with similar frequency, usually in the sixth and seventh decade of life [1]. More than half of the patients present no symptoms, and lesions in the lungs are detected incidentally during follow-up radiological tests. For the other half of the patients, the disease usually manifests itself with dyspnoea and chest pain. Solitary fibrous tumours are usually well limited, benign lesions. Malignant variants with a tendency towards recurrence and metastases occur significantly less often (10–20%) [1]. An evaluation of the tumour's traits in radiological, pathological, and immunohistochemical testing allows for the diagnosis of its malignant character. The malignant form of the tumour is abundant in cells, with ample polymorphism and an increased mitotic activity — a mitotic index above four mitoses per large field of view, with the presence of widespread necrosis and bleeding. The basic treatment method for the SFT is excision [1]. In about 20–30% of patients, local recurrence or spreading may occur — in such a case there is no local treatment option, and systemic treatment must be considered [2]. Data pertaining to systemic treatment are limited; the present work aims to review the literature and summarise the knowledge on the topic of systemic treatment in solitary fibrous tumours of the pleura.

Case report

In August 2013, a 55-year-old female presented at the oncology clinic, with a history of mediastinal tumour that was excised and diagnosed as a malignant SFT. The patient was in good condition (grade 1 on the ECOG scale), presenting no weight loss, and obese (weighing 130 kg). She had a history of hypertension. Presenting complaints included weakness and sporadic cough lasting for several months. Physical examination and routine laboratory testing conducted on the day of the visit revealed no clinically significant abnormalities. Due to a positive surgical margin (R1), the patient

was qualified for radical adjuvant radiation. Intensity Modulated Radiation Therapy (IMRT) was applied to the right pleural area up to a total dose of 5600 cGy, in 28 fractions of 200 cGy each. After the completion of radiotherapy, the patient remained under observation. Two years after the diagnosis, in a control CT scan of the thorax, progressive disease (PD) was detected in the form of three small tumours of the left lung. A wedge resection was performed, with a histopathological confirmation of the recurrence of an SFT. Subsequently, in January and March of 2016, the patient underwent a thoracotomy due to the presence of further lesions in the lungs. In a CT of the thorax conducted two months after surgery, another recurrence was noted, in the form of numerous lesions in the lungs with maximum dimensions of 20 × 15 mm. Due to a lack of radical treatment possibilities, after a multi-specialist consultation, the patient was qualified for palliative chemotherapy with cisplatin (80 mg/m^2) in conjugation with doxorubicin (40 mg/m^2) at 21-day intervals. Four courses of treatment were applied, attaining stable disease (SD). In November 2016 imaging showed another instance of progressive disease. The patient remained in good condition. Tests such as ECG, echocardiography and blood biochemistry showed no abnormalities that would be contraindications of another course of systemic treatment. Treatment with pazopanib was initiated at a dose of 800 mg/day, attaining SD once again. The treatment was continued for a year, until progression. In November 2017, at a multi-specialist session, progressive disease was confirmed at level 1.1 according to the RECIST criteria (Response Evaluation Criteria in Solid Tumours) — a single metastatic lesion appeared in segment IV of the liver. Stereotactic radiotherapy was applied (5000 cGy in five fractions at 1000 cGy), and subsequently chemotherapy with the use of gemcitabine and docetaxel was initiated. After the third treatment cycle, PD was found. The chemotherapy was changed to a doxorubicin, dacarbazine, and cyclophosphamide regimen. In May of 2018 PD was noted once more in the thorax and abdomen. Another line of chemotherapy using ifosfamide showed no effect. The patient remains in good overall condition (ECOG-1). The patient complained only of an increase in exercise intolerance. Previous treatment was conducted with no significant complications.

Discussion

Singular fibrous tumours are usually well-limited benign lesions, with malignant forms occurring significantly less often (10–20%) [1]. Benign SFTs of the thorax are characterised by a high cure rate, with the rate of local recurrence being 8% [1]. The rate of recurrence in the case of a malignant SFT reaches 14–68%, usually in the first two years of observation (even after radical resection) [1, 2]. However, recurrences can also occur even after 17 years [3]. Metastases within the thorax are detected in 0–36% of patients, and metastases outside of the thoracic cavity occur in 0–19% of patients with this diagnosis. The most common sites of metastasis are the lungs and the liver [1]. Less commonly, it metastasises to the mediastinum, pancreas, kidney, and bone [1]. The evaluation of the tumour in imaging, and pathological and immunohistochemical testing allows for the prediction of its malignant character. There are classifications that evaluate not just the histological type (benign/malignant form), but also the type of growth that the tumour is presenting (pedunculated *vs.* wide-based). They were proposed as a means of predicting recurrence after surgical treatment [1]. The rate of recurrence ranges from 2 to 63%, depending on the attributed grade. A complete resection of the primary lesion still remains the most important prognostic factor [3]. Metastatic or locally recurring SFTs may require repeated surgical treatment, radiotherapy, or systemic treatment. The preferred method of treatment in the case of localised lesions is local treatment. Solitary fibrous tumours are commonly considered to be neoplasms of low chemotherapeutic susceptibility [4]. The present work aims at a review of the literature pertaining to the systemic treatment of SFTs of the pleura.

Chemotherapy

The role of chemotherapy was evaluated in a retrospective work including a group of 21 patients with advanced SFT, unqualified for surgical treatment [4]. Most patients were Caucasian (81%), and the average age was 56 years. The most common sites of the primary lesion were the abdomen and pelvis. In 19% of patients, the lesions occurred primarily in the pleura of lungs. Primarily advanced disease occurred in 81% of the patients, and local recurrence affected 5% of patients. Chemotherapy as the first line of treatment was prescribed in 72% of the study participants. 24% of them received the second line of treatment, and one patient received the third line of chemotherapy. Fifteen patients (60%) received doxorubicin-based chemotherapy as the first line of treatment. The most commonly applied regimen was doxorubicin (75 mg/m^2) with ifosfamide (10 g/m^2). About 7% of the patients received doxorubicin and cisplatin chemotherapy. The other regimens and treatment responses are presented in Table 1 [4]. No patient attained objective response, no matter the applied regimen. 89% of the patients who received the first line of chemotherapy achieved stable disease, with 31% achieving stable disease for longer than six months. After the second line of treatment, 67% of patients achieved stable disease. Median progression-free survival time for the first line of chemotherapy was 4.6 months (95% CI 3.7–5.6 months) [4]. In conclusion, the authors point

Table 1. Chemotherapy response evaluated according to the RECIST criteria RECIST 1.1 [4]

Chemotherapy regimen	SD — N (%)	PD — N (%)
First-line treatment	16 (89%)	2 (11%)
Doxorubicin regimen	14	1
Doxorubicin + ifosfamide		
Doxorubicin + dacarbazine		
Doxorubicin + cisplatin		
Doxorubicin in monotherapy		
Gemcitabine regimen	1	1
Gemcitabine+ docetaxel		
Gemcitabine in monotherapy		
Paclitaxel	1	1
Second-line treatment	4 (67%)	2 (33%)
Gemcitabine in monotherapy		
Paclitaxel in monotherapy		
Third-line treatment	0 (0%)	1 (100%)
Gemcitabine		

PD — progressive disease; SD — stable disease

Table 2. Choi response criteria

	Choi
CR	Disappearance of all target lesions
PR	≥ 10% decrease tumour size or ≥ 15% decrease in tumour attenuation at CT
SD	Does not meet criteria for CR, PR, PD
PD	≥ 10% increase in sum of longest diameters of lesions does not meet the criteria for partial response by virtue of tumour attenuation, new intratumoural nodules

CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease

out the role of chemotherapy as a therapeutic option with patients with locally advanced or metastatic SFT enabling disease control.

Trabectedin is an alkaloid extracted from the sea squirt *Ecteinascidia turbinata.* The substance binds to the minor groove of the DNA helix, and its biological mechanism of action involves modulating transcription factors and interaction with proteins responsible for repairing DNA [5]. Trabectedin is a drug registered for the treatment of patients with diagnoses of advanced soft tissue sarcoma. In Poland, contrary to many other EU countries, this drug is reimbursed only for its liposarcoma and leiomyosarcoma subtypes [5]. In a case report of a 39-year-old male diagnosed with advanced SFT, trabectedin was used after a failed first-line treatment intervention. The drug was administered at a dose of 1.5 mg/m^2 in 21-day intervals. After the third course of treatment, a decrease in the size of the metastatic lesions in the lungs was observed [3]. In a French study the treatment effectiveness of trabectedin was evaluated for 11 patients with diagnoses of advanced SFT (the second and third line of treatment) [6]. PR was achieved with one patient (9.1%) and SD for seven patients (72.7%). Median progression-free survival time was 11.6 months. Three patients (27.3%) exhibited toxicity at level 3 or higher — mainly haematological and hepatic toxicity (increased hepatic enzyme activity) [6].

Molecular-guided therapy

Pazopanib is a multi-kinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and stem cell growth factor receptor (KIT). The effectiveness of pazopanib in the treatment of SFTs in preclinical and clinical trials was evaluated by Stacchiotti et al. [7]. In the paper, pazopanib showed lower antitumour activity in mouse models (in comparison to sorafenib, sunitinib, regorafenib, axitinib and bevacizumab). Among the six patients who received pazopanib, three achieved SD and three PD (as evaluated with RECIST criteria). All PD cases were patients with a malignant form of SFT. Evaluating the response with Choi criteria (Table 2), one achieved partial response, two cases of SD, and three cases of PD. Median progression-free survival was three months (1–15 months) [7]. The effectiveness of pazopanib in treating soft tissue sarcomas (including SFTs) was also assessed in the PALETTE analysis [8]. This analysis was an international, multicentre, double-blind, placebo-controlled phase III trial. It compared treatment

responses *vs.* placebo of patients with advanced disease after at least one line of chemotherapy. The patients were randomly assigned to one of two groups: those receiving placebo (n = 123) or those receiving pazopanib at a dose of 800 mg once a day (n = 246). All of them had undergone anthracycline treatment. Median PFS was 4.6 months (95% CI 3.7–4.8 months) for pazopanib and 1.6 months (0.9–1.8) in the placebo group (HR, hazard ratio 0.31, 95% CI 0.24–0.40; $p < 0.0001$). The differences in overall survival were not substantial between the groups ($p = 0.25$) and were: 12.5 months in the pazopanib arm and 10.7 months (median) in the placebo arm. 67% of patients who received pazopanib achieved SD (38% in the placebo group). The treatment was well tolerated. The most commonly reported side effects were fatigue (65%), diarrhoea (58%), nausea (54%), weight loss (48%), and arterial hypertension (41%) [8]. In Poland, because of this research, it is possible to use pazopanib to treat advanced (unresectable or metastatic) sarcomas within the National Health Fund (NFZ) drug program. In 2018, a paper evaluating the effectiveness and safety of pazopanib treatment in patients with a diagnosis of recurrent or metastatic SFT as the first or second line of treatment was published [9]. The response was graded according to RECIST and Choi criteria. The responses were, respectively, 0% and 50%, depending on the applied response criteria. The percentage of patients who achieved disease control was 88.9% and 75%, respectively. Median PFS was 6.2 months (95% CI 3.2–8.8 months). Two patients (22.2%) exhibited a level 3 or higher increase in hepatic enzyme activity [9]. A different analysis presented the effects of pazopanib application in second-line and third-line treatment [10]. No objective responses to treatment were observed, and SD, being the best response, was observed in three out of six treated patients. Two patients receiving had no PD after six and eight months [10].

From among molecular-guided drugs, promising results were obtained also for sunitinib and figitumumab [11]. Sunitinib is a multi-kinase inhibitor of, among others, the VEGF receptor. Six treated patients (60%) with advanced, chemotherapy-resistant SFT achieved PR (Choi criteria). For most of them the response lasted for longer than six months [11]. Insulin-like growth factor-1 (IGF-1) undergoes excessive expression in some cases of SFT. Treatments with figitumumab, a human monoclonal antibody against the IGF-1 receptor, yields promising results [11].

Chemotherapy + molecular-guided therapy

The effectiveness of combining temozolomide with bevacizumab (VEGF monoclonal antibody) was evaluated retrospectively for 14 patients with locally advanced or metastatic SFT or HPC (haemangiopericytoma) [12]. For three patients the disease was primarily localised in lungs or pleura. Five patients had received earlier chemotherapy. In the work, the patients received temozolomide at a dose of 150 mg/m^2 orally on days 1–7 and 15–21 and bevacizumab at 5 mg/m^2 IV on days 8 and 22 in 28-day cycles. Objective response according to Choi criteria was achieved in 11 (79%) patients. Two (14%) exhibited SD and one (7%) PD. The response was also evaluated using RECIST criteria. This time, most patients (12 patients) achieved SD. Median PFS was 9.67 months (Choi PFS). The most commonly observed toxicity was bone marrow suppression [12].

Immunotherapy

In a case report of a 50-year-old patient with a diagnosis of malignant form of SFT of the pleura, after many lines of systemic treatment (carboplatin + paclitaxel, gemcitabine + docetaxel, temozolomide + bevacizumab), treatment with pembrolizumab was introduced [13]. The drug was administered in two doses at 2 mg/kg IV every three weeks. After two cycles of treatment a partial regression of lesions was achieved. The patient is currently continuing the therapy (the last entry — 31 cycle) and is tolerating the treatment very well [13].

About 20% of patients with diagnosed SFT experience local recurrence or distant metastases [12]. The first line of treatment should be resection of lesions, which is not always possible. Available options for treating nonresectable tumours are limited. Radiotherapy can only be used in selected cases. Chemotherapy using doxorubicin and ifosfamide is used in many subtypes of soft tissue sarcomas. Another treatment regimen can be a combination of gemcitabine and docetaxel. However, objective responses to standard chemotherapy treatments are rarely reported [12]. In patients treated with first-line anthracyclines we can consider using pazopanib. Promising results can also be found for other molecular-guided drugs [11, 12] and immunotherapy [13]. However, further research is needed for larger groups of patients, which could confirm the effectiveness of these therapies. The presented patient, after an attempt to treat her locally, finally required systemic treatment. The applied chemotherapy regimens resulted in only short-term disease stabilisation or progression, which confirms the low sensitivity of SFTs to this form of systemic treatment. Treatment with pazopanib led to SD (RECIST criteria 1.1) that was maintained for a year. Unfortunately, retrospective evaluation with Choi criteria was not possible. Currently, the patient is experiencing another PD. She remains under observation and symptomatic care. We can ask ourselves whether the application of consecutive lines of systemic treatment was appropriate. We do not have sufficient information regarding the effects of chemotherapy on

general survival of patients with diagnosed SFT of the pleura, and the PALETTE analysis showed that the differences in overall survival of patients in both groups were statistically insignificant. The presented patient tolerated the treatment very well and she remains in overall good condition. However, we are unable to assess if the applied treatments changed her prognosis and whether we should consider the significantly longer progression-free time and/or the increase in objective response as clinically significant.

References

1. Chick JF, Chauhan NR, Madan R. Solitary fibrous tumors of the thorax: nomenclature, epidemiology, radiologic and pathologic findings, differential diagnoses, and management. AJR Am J Roentgenol. 2013; 200(3): W238–W248, doi: 10.2214/AJR.11.8430, indexed in Pubmed: 23436868.
2. Kalebi AY, Hale MJ, Wong ML, et al. Surgically cured hypoglycemia secondary to pleural solitary fibrous tumour: case report and update review on the Doege-Potter syndrome. J Cardiothorac Surg. 2009; 4: 45, doi: 10.1186/1749-8090-4-45, indexed in Pubmed: 19689813.
3. Chaigneau L, Kalbacher E, Thiery-Vuillemin A, et al. Efficacy of trabectedin in metastatic solitary fibrous tumor. Rare Tumors. 2011; 3(3): e29, doi: 10.4081/rt.2011.e29, indexed in Pubmed: 22066036.
4. Park MS, Ravi V, Conley A, et al. The role of chemotherapy in advanced solitary fibrous tumors: a retrospective analysis. Clin Sarcoma Res. 2013; 3(1): 7, doi: 10.1186/2045-3329-3-7, indexed in Pubmed: 23663788.
5. Koseła-Paterczyk H, Kozak K, Klimczak A, et al. Skuteczność i bezpieczeństwo stosowania trabektedyny w leczeniu pacjentów, u których rozpoznano zaawansowane tłuszczakomięsaki i mięśniakomięsaki gładkokomórkowe (L-mięsaki). Nowotwory. Journal of Oncology. 2015; 65(6): 451–457, doi: 10.5603/njo.2015.0090.
6. Khalifa J, Ouali M, Chaltiel L, et al. Efficacy of trabectedin in malignant solitary fibrous tumors: a retrospective analysis from the French Sarcoma Group. BMC Cancer. 2015; 15: 700, doi: 10.1186/s12885-015-1697-8, indexed in Pubmed: 26472661.
7. Stacchiotti S, Tortoreto M, Baldi GG, et al. Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour. Eur J Cancer. 2014; 50(17): 3021–3028, doi: 10.1016/j.ejca.2014.09.004, indexed in Pubmed: 25269954.
8. van der Graaf WTA, Blay JY, Chawla SP, et al. EORTC Soft Tissue and Bone Sarcoma Group, PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012; 379(9829): 1879–1886, doi: 10.1016/S0140-6736(12)60651-5, indexed in Pubmed: 22595799.
9. Ebata T, Shimoi T, Bun S, et al. Efficacy and safety of pazopanib for recurrent or metastatic solitary fibrous tumor. Oncology. 2018; 94(6): 340–344, doi: 10.1159/000486623, indexed in Pubmed: 29614488.
10. Levard A, Derbel O, Méeus P, et al. Outcome of patients with advanced solitary fibrous tumors: the Centre Léon Bérard experience. BMC Cancer. 2013; 13: 109, doi: 10.1186/1471-2407-13-109, indexed in Pubmed: 23496996.
11. Stacchiotti S, Negri T, Palassini E, et al. Sunitinib malate and figitumumab in solitary fibrous tumor: patterns and molecular bases of tumor response. Mol Cancer Ther. 2010; 9(5): 1286–1297, doi: 10.1158/1535-7163.MCT-09-1205, indexed in Pubmed: 20457621.
12. Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. Cancer. 2011; 117(21): 4939–4947, doi: 10.1002/cncr.26098, indexed in Pubmed: 21480200.
13. Boothe JT, Budd GT, Smolkin MB, et al. Durable near-complete response to anti-pd-1 checkpoint immunotherapy in a refractory malignant solitary fibrous tumor of the pleura. Case Rep Oncol. 2017; 10(3): 998–1005, doi: 10.1159/000484041, indexed in Pubmed: 29279705.

Maciej Kawecki

Department of Oncology and Radiotherapy, Maria Sklodowska-Curie Institute of Oncology, Warsaw

PARP inhibitors as maintenance treatment for pancreatic cancer patients with germline *BRCA* mutations

Advancements in the treatment of pancreatic cancer during the last two decades have been limited mostly to the introduction of active, multi-drug chemotherapy regimens (such as FOLFIRINOX) or technologies aimed at improving the distribution of classic cytotoxic drugs (e.g. nab-paclitaxel). The introduction of novel approaches that have revolutionised systemic treatment in several types of solid tumours — targeted therapies and immunotherapy — have failed in the field of pancreatic cancer. Results of a single positive trial that evaluated the combination of gemcitabine and erlotinib, a targeted agent aimed at EGFR inhibition, are insignificant from clinical point of view because the improvement in overall survival was less than minimal. Immunotherapy, including both monotherapy and combinations of check-point inhibitors, lack the activity seen in other types of cancer. This is probably mostly due to the specific microenvironment of pancreatic cancer with abundant extra-cellular stroma that create a physical barrier impeding infiltration of immune cells. As a result, the modern treatment of pancreatic cancer still relies on classic cytotoxic drugs, mostly multidrug regimens. Without known predictive factors, we still cannot predict an optimal chemotherapy regimen for a specific patient. The decision between FOLFIRINOX and a combination of gemcitabine with nab-paclitaxel, the two most commonly used regimens in the first-line treatment, depends mostly on the experience of the physician and on local standards. Some retrospective analyses suggest additional benefit from platinum agents in patients with known germline mutations in *BRCA*-family genes. This is based on a deficiency in the homologous recombination repair (HRR) mechanism that is present in cells with *BRCA* mutations, leading to the impairment of the double-strain DNA break repair. Removal of DNA double-strain breaks, created by platinum agents mostly through binding purine bases, requires an efficient HRR mechanism. Combination of inadequate activity of HRR and the presence of platinum compounds may generate a critical amount of DNA damage that induces cell death through apoptosis or necrosis. An analogous effect in generating numerous double-strain DNA breaks in cancer cells with non-functional HRR can be achieved with PARP inhibitors. Blocking PARP protein, responsible for the repair of spontaneous single-strain DNA breaks, allows transformation of single-strain breaks into double-strain breaks when the cell enters its replication phase. Germinal mutations in *BRCA* genes are present in 7–10% of patients with pancreatic cancer, in many cases without familial history of *BRCA*-related cancers. Transferring the results of randomised clinical trials from the general population to patients with germinal *BRCA* mutations, we can assume that the optimal first-line chemotherapy regimen containing platinum agent is FOLFIRINOX. In the classic study published by Conroy in 2011 [1] treatment with FOLFIRINOX lasted at least six months in the absence of earlier disease progression. In clinical practice, achieving a full six months of intensive chemotherapy is difficult and often impossible due to cumulative toxicity. One of the possible solutions is the concept of induction and maintenance chemotherapy, which consists of a short, intensive period of FOLFIRINOX (preferably less than six months) with prompt de-escalation to a less intensive maintenance treatment. This approach was evaluated in the phase II PANOPTIMOX trial [2], which compared full six-month FOLFIRINOX and shortened four-month FOLFIRINOX with LV5FU2 maintenance until disease progression. The results show equivalence of the de-escalation strategy compared to the classic schedule, which is essential for patients poorly tolerating FOLFIRINOX. Unfortunately, despite improved tolerance, the de-escalation strategy failed to improve long-term outcomes, including progression-free survival and overall survival. The search for alternative maintenance strategies inspired the idea of using PARP inhibitors in pancreatic cancer patients with germline mutations in *BRCA* genes. This is based on the molecular mechanisms that provide pre-clinical evidence for the idea and the confirmed activity of PARP inhibitors as a salvage treatment in this population. The achieved results are both a breakthrough, because they provide proof that targeted agents offer significant activity in the treatment of pancreatic cancer, and a disappointment, because no effect on overall survival was seen.

Oncology in Clinical Practice 2019, Vol. 15, No. 3, 190–193. DOI: 10.5603/OCP.2019.0023, ISSN 2450–1654

The presented results were published on 2nd July 2019 in "The New England Journal of Medicine" by Golan et al. [3]. The POLO study was a randomised, double-blinded, phase 3 trial that compared maintenance olaparib (300 mg orally twice daily) with placebo in patients with metastatic pancreatic cancer with known germline mutation in *BRCA1* or *BRCA2* genes, who received at least four months of platinum-based first-line treatment without progression. Recruited patients were randomised in a 3:2 ratio to olaparib or placebo. No cross-over after progression was allowed. The primary endpoint was progression-free survival (PFS), with overall survival (OS) as one of the secondary endpoints. Among 3315 patients screened for eligibility, 247 (7.5%) had *BRCA* mutations, and only 154 patients (4.6% of all screened patients) underwent randomisation. Most of the patients (86% in the olaparib arm and 81% in the placebo arm) received FOLFIRINOX as the first-line treatment. The study met the primary endpoint with median PFS of 7.4 months in patients receiving olaparib as compared to 3.8 months in patients receiving placebo (hazard ratio [HR] for progression or death 0.53; 95% confidence interval [CI] 0.35–0.82; p = 0.004). The achieved result remained significant in all analysed subgroups and was independent of the type of mutation (*BRCA1 vs. BRCA2*). Available results in term of OS are immature (46% of events), but an interim analysis showed no statistically significant difference between both arms (with median OS 18.9 months in the olaparib arm *vs.* 18.1 months in the placebo arm; HR 0.91; 95% CI 0.56–1.46; p = 0.68). In the placebo arm, 14.5% of patients received PARP inhibitor after progression. The response rate was 20% among patients receiving olaparib and 10% among patients receiving placebo, with a median duration of response of, respectively, 24.9 months and 3.7 months. Adverse events grade 3 or higher were seen in 40% of patients in the olaparib arm and in 23% of patients in the placebo arm, with serious adverse events seen in, respectively, 24% and 15% of patients. The most common adverse events in the olaparib group were anaemia and fatigue. Patients receiving olaparib required treatment with interruptions or dose reductions due to adverse events. The rate of patients who discontinued the treatment due to toxicity was 5% in the olaparib arm and 2% in the placebo arm. No treatment-related deaths were seen in either arm. Quality of life analysis showed no significant difference between the olaparib and placebo arm.

The results of the POLO study bring important changes to a certain sub-population of patients with pancreatic cancer. The application of olaparib as a maintenance treatment for patients with known *BRCA* mutations nearly doubled the progression-free survival. This validates PARP inhibitors as an interesting treatment option, justifying evaluation of *BRCA1*/*BRCA2* in all patients with pancreatic cancer as a standard. Additionally, results of the POLO study are the first to show clinically significant improvement with targeted therapies in patients with pancreatic cancer. Unfortunately, several aspects of the study limit its popularity. Firstly, the proportion of patients who qualified for the treatment was more than limited — only 4.5% of all screened patients. Secondly, despite the significant improvement in PFS, we currently cannot confirm that olaparib improves the most important endpoint in oncology — overall survival. Thirdly, treatment with olaparib was associated with a significantly higher rate of at least grade 3 adverse events and serious adverse events, albeit without a negative effect on the quality of life. Nevertheless, the POLO study is one of the most important trials dedicated to patients with metastatic pancreatic cancer in recent years, proving the potential of targeted therapies guided by a proper biomarker. We can expect further trials aimed at expanding the role of PARP inhibitors in the treatment of patients with pancreatic cancer, searching for biomarkers other than *BRCA* germline mutations.

When less is more — optimising systemic treatment for elderly and/or frail patients with gastroesophageal cancers

One of the most fascinating aspects of the annual American Society of Clinical Oncology Congress is the fact that some studies presented only as abstracts often influence clinical practice without the publication of full results. While many presented trials are dedicated to narrow and limited subgroups without greater impact on daily clinical practice, some results affect wide groups of patients and provide evidence to revise daily clinical decisions, especially when dedicated to less systematised areas of modern oncology. One such challenge, with growing significance as the populations of Western countries age, is providing care for elderly and/or frail cancer patients. Frailty syndrome is defined as a state of limited functional reserve, mostly due to a decreased capacity of more than one organ system, which impairs adaptation to stressogenic situations (from physical and psychical perspectives). Despite the fact that frailty syndrome and older age often co-exist, even separately they are demanding and difficult to assess because some elderly patients have sufficient functional reserve and some younger patients are extremely vulnerable due to frailty syndrome. As both elderly and frail patients are

underrepresented in clinical trials, it is important to notice results of trials dedicated solely to this population.

One such study, the phase 3 GO2 trial, was given as an oral presentation and abstract at the 2019 Congress of American Society of Clinical Oncology by Hall et al. [4]. It was a randomised, phase 3 trial that compared different variants of doses of CAPOX in patients with gastroesophageal cancer, who were ineligible to the EOX regimen due to age and/or frailty syndrome. Comparison included three different variants of doses of CAPOX: level A — with oxaliplatin 130 mg/m^2 on day 1 and capecitabine 625 mg/m^2 on days 1–21 of every 21-day cycle; level B — with 80% of doses from level A; and level C — with 60% of doses from level A. The primary endpoint was a comparison of PFS, with OS as one of secondary endpoints. Additionally, the trial included evaluation of composite endpoint (called Overall Treatment Utility; OTU), which included treatment benefit evaluated by a physician, tolerability of treatment, quality of life, and assessment of treatment by the patient. The trial included 514 patients, randomised in a 1:1:1 ratio to all three treatment arms. Median age was 76 years in arm A and arm B and 77 years in arm C. In each arm about 1/3 of patients had performance status (ECOG) 2 or worse, and nearly 80% of patients in each arm had frailty syndrome. Median PFS was 4.9 months in arm A, 4.1 months in arm B and 4.3 months in arm C, which met a prespecified non-inferiority margin for comparison of arm B to arm A (HR 1.09; 95% CI 0.89–1.32) and for comparison of arm C to arm A (HR 1.10; 95% CI 0.90–1.33). Median OS was 7.5 months in arm A, 6.7 months in arm B, and 7.6 months in arm C. In arm C, lower rate of non-haematological adverse events grade 3 or higher was noted (37% in arm C compared to 56% in arm A) as well as better results in terms of combined endpoint OTU. No subgroup benefited from higher doses of chemotherapy.

Results of the GO2 study provide valuable insights into clinical management of elderly and/or frail patients with gastroesophageal cancers. In this group, lower doses of chemotherapy were associated with a reduced rate of adverse events and maintained activity with PFS and OS comparable to standard dosing. Additionally, probably due to the lower rate of non-haematological adverse events, the lowest doses of chemotherapy achieved the best results in a combined endpoint that evaluated, among others, quality of life. Implementation of these results into daily practice may be challenging, especially in health care systems with limited financing, such as in Poland, due to difficulties with evaluation of frailty syndrome. Proper evaluation of frail patients, especially when frailty coexists with older age and other comorbidities, requires competences not common among oncologists and additional time, a resource that is scarce for most practicing oncologists in Poland. Nevertheless, even including the aforementioned difficulties, the improvement of quality of life obtained with decreased intensity of chemotherapy highly valuable and is extremely important in more vulnerable populations, including elderly and frail patients.

Molecular subgroups of low-grade gliomas and effectiveness of PCV chemotherapy — a new predictive factor?

Treatment of primary central nervous system tumours in one of the most demanding fields in oncology. Proper diagnostics, surgical treatment, radiotherapy, and possible systemic treatment not only significantly impacts overall survival, but also defines quality of life. This includes glioblastoma multiforme, a disease characterised by uniquely unfavourable prognosis, which usually requires multimodality treatment, as well as low-grade gliomas in which maintenance of functional capabilities and quality of life is nearly as important as improvement in overall survival. From this perspective, personalisation of treatment and adjustment of intensity according to treatment aims is more than crucial. For low-grade (G2) gliomas with unfavourable prognostic factors — age over 40 years and age under 40 years with subtotal tumour resection, since 2016 and publication of NRG Oncology/RTOG 9802 trial results, standard postoperative treatment consists of radiotherapy and subsequent 48-week PCV (procarbazine, lomustine, vincristine) chemotherapy [5]. The addition of PCV chemotherapy to standard radiotherapy prolonged median OS by nearly six years, increasing rate of 10-year PFS from 21% to 51%. Still, the chemotherapy is intensive, long, and associated with high risk of adverse events, mostly haematological. New analysis of data from the NRG Oncology/RTOG 9802 study, which assessed the newest molecular subgroups of low-grade gliomas, gives the opportunity for further optimisation of treatment in this group of patients.

The report was presented at an oral session and as an abstract on 2019 Congress of American Society of Clinical Oncology by Bell et al. [6]. The analysis included 106 (46%) of 251 patients with grade 2 gliomas, who participated in the NRG Oncology/RTOG 9802 study and who had tumour sample sufficient to evaluated state of IDH1/2 mutation and 1p/19q co-deletion. Mutations

in IDH were present in 75% of analysed patients, with 41% of patients having IDH mutations without 1p/19q co-deletion and 35% of patients having both IDH mutation and 1p/19q co-deletion. In a single-factor analysis no benefit from PCV chemotherapy was seen in patients without IDH mutation, and strong benefit from PCV chemotherapy was seen in patients with IDH mutation without simultaneous co-deletion (HR for PFS 0.32; $p = 0.003$; HR for OS 0.38; $p = 0.013$) as well as in patients with IDH mutation and 1p/19q co-deletion (HR for PFS 0.13; $p < 0.001$; HR for OS 0.21; $p = 0.029$).

Despite the fact that the analysis is post-hoc and include only a limited population, it seems that the role of IDH as a predictive factor for benefit from postoperative PCV chemotherapy in grade 2 gliomas with unfavourable risk factor is strong and promising. Evaluation of IDH mutation, included currently in the standard WHO classification of gliomas, can be a good argument in the discussion with patients in favour of chemotherapy. Implementation of IDH evaluation provides a very rare opportunity for personalised treatment within the current standard of care.

References

1. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer, PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364(19): 1817–1825, doi: 10.1056/NEJMoa1011923, indexed in Pubmed: 21561347.
2. Dahan L, Phelip J, Malicot KLe, et al. FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX). J Clin Oncol. 2018; 36(15_suppl): 4000, doi: 10.1200/jco.2018.36.15_suppl.4000.
3. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline-mutated metastatic pancreatic cancer. N Engl J Med. 2019 [Epub ahead of print], doi: 10.1056/NEJMoa1903387, indexed in Pubmed: 31157963.
4. Hall P, Swinson D, Waters J, et al. Optimizing chemotherapy for frail and elderly patients (pts) with advanced gastroesophageal cancer (aGOAC): The GO2 phase III trial. J Clin Oncol. 2019; 37(15_suppl): 4006, doi: 10.1200/jco.2019.37.15_suppl.4006.
5. Buckner J, Shaw E, Pugh S, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016; 374(14): 1344–1355, doi: 10.1056/nejmoa1500925.
6. Bell E, Won M, Fleming J, et al. Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/RTOG 9802. J Clin Oncol. 2019; 37(15_suppl): 2002, doi: 10.1200/jco.2019.37.15_suppl.2002.