OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2019, Vol. 15, Number 4

ISSN 2450–1654

Ewa Klank-Sokołowska, Mariola Kucharewicz, Marek Z. Wojtukiewicz
Cabozantinib in the treatment of advanced hepatocellular carcinoma patients

Ewa Wrona, Piotr Potemski
A novel immunotherapy — the history of CAR T-cell therapy

Dariusz Pysz-Waberski, Weronika Bulska-Będkowska, Ewa Wachuła
Treatment of chronic pain in oncology: cooperation between the oncologist and psychooncologist

Kamila Patrycja Kidrycka, Justyna Burzyńska-Śliwowska, Rafał Maksim, Andrzej Namiot, Marek Z. Wojtukiewicz, Ewa Sierko
Angiosarcoma — a malignant neoplasm secondary to radiotherapy for breast cancer in a female patient following breast-conserving treatment — a case report

Marcin J. Napierała, Anna M. Czarnecka
Mucosal melanoma — clinical presentation and treatment based on a case series

Katarzyna Kryszczyszyn-Musialik, Grzegorz Słomian, Krzysztof Musialik
Hodgkin's lymphoma with multifocal *Staphylococcus aureus* infection in a 29-year-old male — a case study

VIA MEDICA

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology

https://journals.viamedica.pl/oncology_in_clinical_practice

Oncology in Clinical Practice (ISSN 2450–1654) 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

18-0237.016.001

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 4

REVIEW ARTICLES

Cabozantinib in the treatment of advanced hepatocellular carcinoma patients
Ewa Klank-Sokołowska, Mariola Kucharewicz, Marek Z. Wojtukiewicz 195

A novel immunotherapy — the history of CAR T-cell therapy
Ewa Wrona, Piotr Potemski 202

Treatment of chronic pain in oncology: cooperation between the oncologist and psychooncologist
Dariusz Pysz-Waberski, Weronika Bulska-Będkowska, Ewa Wachuła..... 208

CASE REPORTS

Angiosarcoma — a malignant neoplasm secondary to radiotherapy for breast cancer in a female patient following breast-conserving treatment — a case report
Kamila Patrycja Kidrycka, Justyna Burzyńska-Śliwowska, Rafał Maksim, Andrzej Namiot, Marek Z. Wojtukiewicz, Ewa Sierko..... 217

Mucosal melanoma — clinical presentation and treatment based on a case series
Marcin J. Napierała, Anna M. Czarnecka 223

Hodgkin's lymphoma with multifocal *Staphylococcus aureus* infection in a 29-year-old male — a case study
Katarzyna Kryszczyszyn-Musialik, Grzegorz Słomian, Krzysztof Musialik..... 231

VIA MEDICA

REVIEW ARTICLE

Ewa Klank-Sokołowska[1], Mariola Kucharewicz[1], Marek Z. Wojtukiewicz[1, 2]

[1]Department of Clinical Oncology, Comprehensive Cancer Centre of Białystok, Poland
[2]Department of Oncology, Medical University of Bialystok, Poland

Cabozantinib in the treatment of advanced hepatocellular carcinoma patients

Address for correspondence:
Prof. dr hab. n. med.
Marek Z. Wojtukiewicz
Klinika Onkologii Uniwersytet Medyczny
w Białymstoku
Białostockie Centrum Onkologii
ul. Ogrodowa 12, 15–027 Białystok
e-mail: onkologia@umb.edu.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 195–201
DOI: 10.5603/OCP.2019.0007
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed malignancy in the world, with the number of cases steadily increasing. Currently, around 850,000 new cases are diagnosed annually. In the majority of patients, HCC is diagnosed at an advanced stage mainly due to the lack of early symptoms. Risk factors for HCC are well known. HCC usually develops in cirrhotic liver; the exception is a form of fibrolamellar carcinoma arising in healthy liver. Hepatocarcinogenesis is a multistage process in which many pathways of intracellular signal transduction are disturbed, which leads to various biological characteristics of the disease. During foetal life, liver cells produce multiple factors, e.g. epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), or platelet-derived growth factor (PDGF), which play a significant role in organogenesis. In adults, the production of many of the factors decreases or does not exist. As a result of organ damage (e.g. after injury), hepatocytes start the synthesis again, but only temporarily. In a chronically damaged liver, a dysregulation of the production of these factors takes place, it is continuous and leads to hepatocarcinogenesis. Understanding the HCC pathogenesis has allowed the synthesis of compounds that can directly interfere with the molecular pathways associated with the growth and progression of tumours. Cabozantinib (an oral tyrosine kinase inhibitor) targets VEGF, MET, and AXL receptors. It may be an option in patients with HCC with disease progression after one or two lines of systemic treatment (e.g. after sorafenib therapy). The use of cabozantinib in the treatment of patients with advanced HCC was evaluated in a prospective phase III study, which demonstrated prolongation of overall survival (OS) and progression-free survival (PFS) compared to patients receiving placebo. Based on the results of the study, the use of cabozantinib provides an opportunity to further improve treatment outcomes in patients with advanced HCC.

Key words: hepatocellular carcinoma, cabozantinib, multikinase inhibitor, signal transduction pathways, treatment outcomes

Oncol Clin Pract 2019; 15, 4: 195–201

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Hepatocarcinogenesis is a complex, multistage process, in which the disorders of many intracellular transduction pathways occur, subsequently leading to heterogenous biological characteristics of the disease. During foetal life, many growth factors are produced by hepatocytes and this plays a significant role in organogenesis — these are epidermal growth factor (EGF), insulin-like growth factors (IGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and transforming growth factor-α and -β (TGF-α, -β). In the healthy liver of an adult human the production of many of them is reduced to a minimum or does not exist. In turn, when regenerative processes after organ damage (e.g. injury) require the production of these factors, adult hepatocytes synthesise them for a transitional period (EGF, TGF-α, IGF, and VEGF). However, this process is dysregulated

in chronically damaged liver, leading to permanent mitogenic signalling. Like other growth factors (FGF, PDGF), HGF is produced and released from sources other than hepatocytes (e.g. activated hepatic stellate cells, myofibroblasts, endothelial cells, Kupffer cells, and bile duct epithelium), which can contribute to hepatocarcinogenesis. There is no single dominant signal pathway in the pathogenesis of HCC; however, the introduction of molecular target-directed drugs (targeted therapies) significantly expanded the possibilities of systemic therapy of patients with HCC [1, 2].

The first drug with documented impact to extend overall survival (OS) in patients with HCC in advanced clinical stages was sorafenib, a small-molecule multikinase inhibitor. Clinical efficacy has also been confirmed for regorafenib in the second-line treatment. Regorafenib has molecular targets similar to sorafenib — in patients with advanced HCC after sorafenib failure it showed a significant prolongation of OS by almost three months compared to the control group.

A novel drug with proven effectiveness in the treatment patients with HCC is cabozantinib, an oral tyrosine kinase inhibitor targeted against VEGFR, MET, and AXL. Cabozantinib is indicated for use as monotherapy in adult patients with HCC previously treated with sorafenib. The aim of the study is to present the value of cabozantinib in patients with advanced HCC.

Epidemiology

The most common primary liver cancer is HCC (approximately 85–90%), which accounts for about 4% of all newly diagnosed cancers in the world and is the sixth cancer in terms of prevalence worldwide (about 850,000 new cases annually) and the tenth cause of cancer-related deaths. HCC morbidity is constantly increasing. Gender diversity is observed — HCC applies more than twice as much to men than to women. In Poland about 3000 new cases are diagnosed annually. Unlike other human malignancies, risk factors for HCC are well understood [2–7]. There is also clear geographical differentiation of HCC, which is undoubtedly related with exposure to hepatitis B (HBV) and C virus (HCV) infections. More than 80% of all HCC cases occur in developing countries, mainly in China and Southeast Asian countries and in sub-Saharan Africa. In Western countries the incidence of HCC is low except for in Southern Europe, where morbidity among men is higher.

The risk of developing HCC increases with age. The highest incidence is observed in people aged around 50–60 years, but some young people at the age of 20–30 years are also affected; they have a rarely occurring form of so-called fibrolamellar carcinoma (FLC).

Aetiology

In 70–90% of cases, HCC develops on the grounds of liver cirrhosis, caused by chronic hepatotropic virus infection (HBV, HCV) or toxic liver damage (alcohol, *nonalcoholic fatty liver* disease [NAFLD], aflatoxin — produced by *Aspergillus flavus*), and it is seen much less often metabolic diseases (especially hemochromatosis — about 300-fold increased risk of HCC) and alpha-1 antitrypsin deficiency. Other factors that increase HCC risk are associated with obesity and insulin resistance. Research is currently underway to determine the impact of genetic disorders on HCC development. Mutations, translocations, amplifications, deletions within suppressor genes (*TP53*, *DLC1*, Wnt pathway), oncogenes and growth factors (EGFR, VEGFR, Ras, mTOR pathway, HEDGEHOG, HGF, IGF), and cell cycle regulators (cyclin-dependent kinase inhibitor 2A [p16] or cell cycle regulator p27). Understanding genetic disorders allows the use of targeted therapies. The targets for molecular drugs are intracellular signalling pathways responsible for cell proliferation and tumour growth, but also influencing tumour angiogenesis and dissemination [1, 7, 8].

HCC development is a complicated, multistage process. A transformation from a regenerative nodule into cirrhosis, through the dysplastic nodule, to cancer usually takes many months. Enlarging the lesion to about 2 cm in diameter takes about 12 months [9–11].

Pathology

Hepatocellular cancer is adenocarcinoma in a single-focal, multifocal, or disseminated infiltration form. It can have various degrees of histological maturity — from G1 (reminiscent of normal hepatocytes) to G4 (undifferentiated). FLC is a specific type, found mainly in young people, with no relation to cirrhosis, appearing in unchanged liver without connection to viral infection, and characterised by increased AFP serum concentration.

Diagnostics

Symptoms

Early HCC symptoms are unspecific. They may result from coexisting liver cirrhosis. The course of liver cirrhosis in compensated phase may be asymptomatic or minimal symptoms may be found. General symptoms include: asthaenia, loss of appetite, weight loss, low-grade fever, nausea, vomiting, diarrhoea, and pain in the right subcostal region of the abdomen or epigastrium. The liver can be enlarged, hard, painless, and with

nodular changes. Increasing portal hypertension leads to development of collateral circulation, oesophageal varices, haemorrhoids, and characteristic "Medusa's head" (widened capillary network in the chest and abdominal wall). Impairment of hepatic function can lead to thromboembolic complications or haemorrhagic diathesis. The symptoms may also include jaundice, ascites, or encephalopathy in advanced states. In the course of HCC, symptoms of paraneoplastic syndromes can occur: dermatomyositis syndromes, gynecomastia, polyglobulia, hypercalcaemia, hypercholesterolaemia, hypoglycaemia, or dysfibrinogenaemia [10, 12].

Laboratory tests

In patients with HCC, abnormal results of laboratory tests are observed. In the complete blood count (CBC) some features of anaemia are observed, as well as thrombocytopaenia, that can transform into thrombocythaemia. Coagulation system disorders are also present (reduced prothrombin plasma level, prolonged activated partial thromboplastin time [APTT]), as well as disorders of lipid (hypocholesterolaemia, sometimes leading to hypercholesterolaemia) and protein (hypoalbuminaemia, reduced total protein plasma level) metabolism. Hyperbilirubinaemia is observed, increased aminotransferase levels with common predominance of aspartate aminotransferase (AST) over alanine aminotransferase (ALT) — de Ritis ratio > 1, glucose intolerance or type 2 diabetes, and, rarely, hepatorenal syndrome (HRS).

The only serological marker used in HCC diagnosis is AFP serum concentration [10, 12]. The value of AFP does not show a close relationship with HCC stage. In a significant group of patients with HCC, an increased AFP (α-fetoprotein) concentration is observed, but in approximately 40% of patients there is no increase in the concentration of this protein. About 30% of patients with cirrhosis may have an elevated AFP concentration without HCC. In patients with FLC the concentration of AFP may be normal.

Non-invasive diagnostics

In the majority of patients the diagnosis of HCC is based on imaging examinations. The most commonly used method in the initial diagnosis, especially in surveillance of patients with cirrhosis, is abdominal ultrasound examination (USG). The sensitivity of this method ranges between 65 and 80%, and the specificity is above 90%. The basic diagnostic methods include three-phase computed tomography (CT) examination with contrast medium and magnetic resonance imaging (MRI). The radiological picture is characteristic: there is contrast enhancement in the arterial phase of the study and delayed contrast washout during venous and delayed phases. According to the guidelines, a typical radiological image justifies HCC diagnosis without histopathological examination [13–15].

Positron emission tomography (PET) in combination with CT (PET-CT) is not recommended for recognition of early cancer forms but may be useful in later stages to exclude a retrohepatic tumour location.

Invasive diagnostics

HCC diagnosis is based on histological or — less valuable — cytological examination. As recommended by experts and European guidelines (EASL 2018 guidelines), in the case of cirrhotic liver with nodule below 1 cm, which neither changes its nature nor grows, abdominal USG should be repeated every four months. If the tumour grows to a diameter of 1–2 cm, detailed imaging diagnostics (CT, MRI) should be performed. A change of 1–2 cm requires confirmation in two imaging tests with contrast. In the case of nodules greater than 2 cm, a typical radiological image (as described above) in a single imaging study is sufficient to diagnose HCC.

Clinical staging of HCC helps in selecting the optimal treatment strategy. In addition to the need to perform imaging tests, it is also required to assess patient's performance status (PS) and liver function. There are several systems for HCC clinical classification. The TNM classification only assesses the stage of the disease and does not take into account the accompanying hepatic impairment according to Child-Pugh scale. Okuda staging system (Okuda's scale), including information about tumour and liver function, is currently rarely used. In Europe the most popular classification is the Barcelona Clinic Liver Cancer (BCLC) staging system, which assesses all of aforementioned factors (tumour stage, liver efficiency according to the Child-Pugh scale, and PS). The BCLC classification divides patients into five categories (0, A, B, C, and D). The BCLC division is helpful when assessing patients' eligibility for treatment [3, 4, 13, 16–18].

Surgical treatment

Eligibility criteria of HCC patients for surgical treatment and transplantation are highly restrictive but give a chance of a complete cure. Cancer resection in cirrhotic liver may be considered in patients with BCLC stage 0 or A. In patients without cirrhosis, surgery is the treatment of choice because the resection of even a large volume of the organ does not put the patient at risk of liver failure. Classical eligibility criteria for liver transplantation in patients with HCC are the so-called

Milan criteria: patients with one nodular change in the liver less than 5 cm or a maximum of three lesions in the liver not exceeding 3 cm can be qualified for transplantation. In practice, extended criteria are often used, the so-called "up to seven" criterion — the size of the largest lesion expressed in centimetres and the number of remaining lesions summed to a maximum of seven [13, 19–21].

Local methods of treatment

In a properly selected group of patients with recurrent diseases after surgery or ineligible for resection or transplantation a significant improvement of prognosis, and even long-term remission, can be obtained using local methods of treatment, which include: radiofrequency ablation (RFA), percutaneous ethanol injection therapy (PEIT), radioembolisation, transarterial embolisation (TAE), or cryoablation [22–24].

Systemic treatment

Advances in understanding the pathogenesis of HCC have led to the development of drugs that can interfere directly with the molecular pathways associated with cancer growth and progression. Sorafenib has proven impact on OS in HCC patients; it is an oral small-molecule inhibitor of many tyrosine kinases (Raf, VEGFR, PDGR-b, KIT, FTL-3, RET) and is characterised by anti-angiogenic and anti-proliferative activity. The basis for the registration of sorafenib for use in HCC treatment was an international, multi-centre phase III clinical trial with the acronym SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol). The results of the study showed a significant OS improvement in HCC patients treated with sorafenib, compared to the placebo group. In total, 602 patients with advanced HCC were enrolled in the study (approximately 90% from European sites). Treatment with sorafenib was rarely associated with an objective response to treatment – the partial response (PR) rate was seen in 2.3% of patients only; more often stabilisation of the disease (SD) was observed (about 71%). The median OS in sorafenib patients was 10.7 months, that is almost three months longer than in the control group [25, 26]. In another phase III clinical trial with similar design to the SHARP study, the efficacy of sorafenib in the Asian population was evaluated; a significant reduction of the disease progression risk (by 42%) and risk of death (by 33%) were observed. Note the difference in statistical power of both studies and the difference in the aetiology of HCC — in the Asian study patients with hepatitis B virus (HBV) constituted about 75% of the study population, while in the European study it was about 30% of patients. The Asian study also included patients in a worse general condition and with more advanced HCC compared to the European study; hence, both prognosis and treatment results in Asian countries were generally worse [27, 28]. In Poland, sorafenib is reimbursed within a drug program. This agent is indicated in the treatment of patients with HCC with advanced disease, which prevents surgical treatment of patients with relapse after radical surgery, after failure of previously used local treatment methods, or when they are unavailable.

Another option of systemic treatment of patients with HCC is regorafenib, which is a multi-kinase inhibitor with similar molecular targets to sorafenib (the structure differs only by one substituent). Regorafenib is indicated for second-line treatment in patients with advanced HCC, who received sorafenib in the first-line therapy with good clinical tolerance but, progression of the disease was found after a beneficial period. In a clinical trial regorafenib was compared with placebo, and OS was the main efficacy outcome assessed. Regorafenib was shown to prolong the OS — the median was 10.6 months, compared with 7.8 months in placebo group [29]. Currently in Poland regorafenib treatment is not reimbursed.

A new drug with proven efficacy targeting the molecular pathways associated with tumour growth and HCC progression is cabozantinib [30, 31]. Cabozantinib may be considered in patients with disease progression, who have received one or two systemic treatment lines and have normal liver function and performance status 0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale. On November 12, 2018, the European Medicines Agency (EMA) approved cabozantinib for use as monotherapy in the treatment of adult HCC patients who had previously received sorafenib.

Cabozantinib is an oral non-selective, multi-kinase inhibitor directed against VEGF receptor type 2 (VEGFR2), the *mesenchymal epithelial* transition factor *receptor* (*Met*), and AXL receptor tyrosine kinase (Fig. 1) [32, 33]. Through the inhibition of tyrosine kinases, cabozantinib affects processes associated with tumour growth, angiogenesis, metastasis, bone remodelling, and drug resistance. Effects on VEGF pathway are a known therapeutic target in HCC, but clinical benefits are inadequate. Inhibition of additional intracellular transmission pathways can successfully improve the effectiveness of treatment. Similarly to VEGR, the MET and AXL tyrosine kinase receptors are induced by tumour hypoxia and play an important role in tumour biology. The dysregulation of HGF/cMET pathway receptors is crucial for hepatocyte regeneration after liver injury. Both kinases are also involved in the development of resistance to anti-angiogenic therapies. High MET and

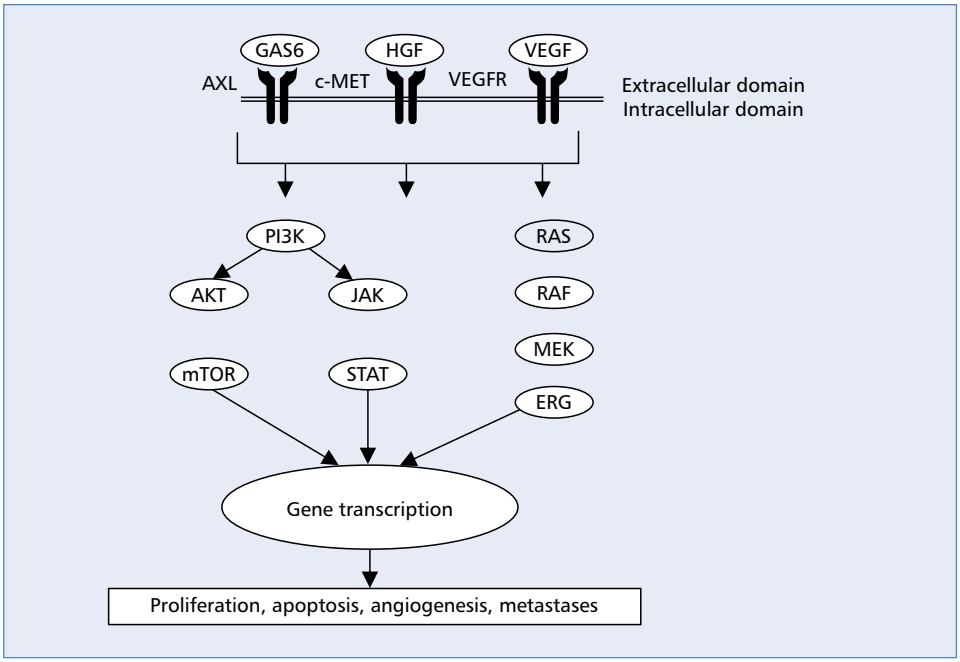

Figure 1. Mechanism of action of cabozantinib

AXL expression may be associated with poor prognosis in HCC patients.

In a phase II randomised clinical trial, cabozantinib showed clinical activity in patients with advanced HCC, and the results were independent of previous treatment (prior sorafenib use — yes or no). The median OS was 11.5 months, and the median progression-free survival (PFS) reached 5.2 months.

Based on the aforementioned results, a phase III double-blind, randomised, placebo-controlled study (CELESTIAL) was performed. Recruitment for the study was conducted in 19 countries from September 2013 to September 2017. The study included 707 patients with advanced HCC, who were ineligible for radical treatment and had previously received sorafenib in first-line treatment. Inclusion criteria were as follows: age over 18 years, ECOG performance status 0–1, Child-Pugh class A, normal kidney function, and absence of abnormalities in haematopoietic function. Patients were allowed to receive one previous treatment line — apart from sorafenib — due to advanced disease. Patients were randomly assigned (2: 1) to a group receiving cabozantinib (n = 470) or a group receiving placebo (n = 237). Randomisation was stratified according to the aetiological factor (HBV with or without HCV, HCV — without HBV, or other), geographical region (Asia or other region), and the presence of extrahepatic metastases and infiltration of large blood vessels. Cabozantinib was administered orally at a daily dose of 60 mg. A treatment disruption or dose reduction to 40 mg and 20 mg was used to control side effects. Treatment was continued until patients had clinical benefit or until unacceptable toxicity occurred. OS was a primary endpoint, and the secondary endpoints included PFS and overall response rate (ORR). The response was assessed based on CT according to RECIST 1.1 criteria every eight weeks, and patients were allowed to continue blinded treatment after radiological disease progression as long as they had clinical benefit. Based on the data analysis, it was found that the median OS in the cabozantinib group was 10.2 months (95% CI [confidence interval]: 9.1–12.0 months) and 8.0 months in the placebo group (95% CI: 6.8–9.4 months). The risk of death decreased by 24% (hazard ratio [HR] = 0.76; 95% CI: 0.63–0.92; p = 0.005). The median PFS in cabozantinib group was 5.2 months (95% CI: 4.0–5.5 months) and 1.9 months in the placebo group (95% CI: 1.9 months). The risk of disease progression decreased by 56% (HR = 0.44, 95% CI: 0.36–0.52, p < 0.001). Objective response rate according to RECIST 1.1 criteria was 4% in the cabozantinib group (18 out of 470 patients achieved PR) and less than 1% in the placebo group (one out of 237 patients). Disease control (PR and SD) was achieved in 64% of patients treated with cabozantinib (n = 300) compared with 33% (n = 79) in the placebo group. In the CELESTIAL clinical trial, the mean treatment duration was 3.8 months in the cabozantinib group and two months in the placebo group. The dose was reduced in 62% of patients receiving cabozantinib (n = 291) and in 13% in the placebo group (n = 30). The average daily dose of cabozantinib was 35.8 mg, and in the placebo group it was 58.9 mg, with median time to

first dose reduction of 38 days, and to first disruption of cabozantinib treatment — 28 days. The majority of complications observed with cabozantinib were analogous to the adverse effects profile observed during treatment with other tyrosine kinase inhibitors with anti-VEGFR activity. The incidence of adverse events (AEs) of any degree was high, e.g. 99% *vs.* 92%, of which there were 68% and 36% grade 3 and 4 AEs, respectively. The most common grade 3 and 4 adverse events in the cabozantinib group were: hand-foot syndrome (palmar-plantar erythrodysesthesia [PPE]) — 17% *vs.* 0%, hypertension — 16% *vs.* 2%, increased transaminases activity — 12% *vs.* 7%, fatigue — 10% *vs.* 4%, diarrhoea — 10% *vs.* 2% [34]. The most frequent cause of dose reduction in patients receiving cabozantinib was PPE (22%), diarrhoea (10%), fatigue (7%), hypertension (7%), and elevated transaminases (6%).

In conclusion, cabozantinib therapy in patients previously treated systemically due to advanced HCC resulted in statistically and clinically significantly longer OS and PFS, compared with patients receiving placebo.

Conclusions

Significant evolution in understanding the molecular pathology of HCC has contributed to the development of drugs targeted on signalling pathways [18, 35]. Pre-clinical and clinical trials are underway to test other options in HCC therapy. Recently, high hopes are associated with immunotherapy, used in various types of cancer. There are currently many clinical trials evaluating the safety and efficacy of new therapies for the treatment of HCC, including nivolumab, pembrolizumab, tremelimumab, and lenvatinib [36–39]. It seems that in the near future this may translate into an improvement in the treatment outcomes in patients with advanced HCC.

References

1. Höpfner M, Schuppan D, Scherübl H. Growth factor receptors and related signalling pathways as targets for novel treatment strategies of hepatocellular cancer. World J Gastroenterol. 2008; 14(1): 1–14, indexed in Pubmed: 18176955.
2. Torre L, et al. Global cancer statistics 2012. Global cancer statistics 2012, CA Cancer J Clin. 2015; 65: 87–108.
3. Galle P, Forner A, Llovet J, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018; 69(1): 182–236, doi: 10.1016/j.jhep.2018.03.019.
4. Vogel A, Cervantes A, Chau I, et al. Hepatocelular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annalos of Oncology. 2018; 29(supl 4): 238–255.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5): E359–E386, doi: 10.1002/ijc.29210, indexed in Pubmed: 25220842.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68(1): 7–30, doi: 10.3322/caac.21442, indexed in Pubmed: 29313949.
7. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007; 132(7): 2557–2576, doi: 10.1053/j.gastro.2007.04.061, indexed in Pubmed: 17570226.
8. Kudo M. Signaling pathway/molecular targets and new targeted agents under development in hepatocellular carcinoma. World J Gastroenterol. 2012; 18(42): 6005–6017, doi: 10.3748/wjg.v18.i42.6005, indexed in Pubmed: 23155330.
9. Kojiro M, Roskams T. Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis. 2005; 25(2): 133–142, doi: 10.1055/s-2005-871193, indexed in Pubmed: 15918142.
10. Simon K. Etiopatogeneza raka wątrobowokomórkowego 2012. Kompendium postępowania w nowotworach wątroby. 2012: 12–18.
11. Górnicka B, Nasierowska-Guttmejer A. Rak wątrobowokomórkowy — podstawy diagnostyki morfologicznej. 2014; 18(1): 9–13.
12. Pazgan-Simon M, Zuwała-Jagiello J. Kompendium postępowania w nowotworach wątroby. 2012: 19–21.
13. Krawczyk M, Wasilewicz M, Hartleb M, et al. Rozpoznanie i leczenie raka wątrobowo komórkowego. Rekomendacje sekcji hepatologicznej PTG. Gastroenterologia Praktyczna. 2016.
14. Krzakowski M, Zieniewicz A, Habior A, et al. Rak wątrobowokomórkowy — rozpoznanie i leczenie. Med Prakt Onkol. 2009; 6: 73.
15. Ayuso C, Rimola J, García-Criado A. Imaging of HCC. Abdom Imaging. 2012; 37(2): 215–230, doi: 10.1007/s00261-011-9794-x, indexed in Pubmed: 21909721.
16. National Comprehensive Cancer network. NCCN clinical practice guidelines in oncology: hepatobiliary cancers, vers. 2017; 4.
17. Bruix J, Sherman M, Llovet JM, et al. EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona — 2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001; 35(3): 421–430, indexed in Pubmed: 11592607.
18. Akoad ME, Pomfret EA. Surgical resection and liver transplantation for hepatocellular carcinoma. Clin Liver Dis. 2015; 19(2): 381–399, doi: 10.1016/j.cld.2015.01.007, indexed in Pubmed: 25921669.
19. Marín-Hargreaves G, Azoulay D, Bismuth H. Hepatocellular carcinoma: surgical indications and results. Crit Rev Oncol Hematol. 2003; 47(1): 13–27, indexed in Pubmed: 12853096.
20. Małkowski P, Chmura A, Pacholczyk M, et al. Przeszczepienie wątroby — metody klasyczne i warianty. Med Sci Rev Hepatol. 2005: 119–126.
21. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005; 25(2): 181–200, doi: 10.1055/s-2005-871198, indexed in Pubmed: 15918147.
22. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg. 2004; 240(5): 900–909, indexed in Pubmed: 15492574.
23. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004; 127: S179–88.
24. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003; 37(2): 429–442, doi: 10.1053/jhep.2003.50047, indexed in Pubmed: 12540794.
25. Llovet JM, Ricci S, Mazzaferro V, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359(4): 378–390, doi: 10.1056/NEJMoa0708857, indexed in Pubmed: 18650514.
26. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. Expert Rev Anticancer Ther. 2009; 9(6): 739–745, doi: 10.1586/era.09.41, indexed in Pubmed: 19496710.
27. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10(1): 25–34, doi: 10.1016/S1470-2045(08)70285-7, indexed in Pubmed: 19095497.
28. Tokajuk P, Uścinowicz A, Wojtukiewicz MZ. Sorafenib w leczeniu chorych na zaawansowanego raka wątrobowokomórkowego. Contemp Oncol. 2014; 18(1): 41–46.
29. Bruix J, Qin S. Merle Ph., Granito A . Regorafenb for patiens with hepatocellular carcinoma who progresse on sorafenib treatment (RESORCE): a randomised, double- blind, placebo- controlled, phase 3 trial. Lancet. 2017; 389: 56–66.
30. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018; 379(1): 54–63, doi: 10.1056/NEJMoa1717002, indexed in Pubmed: 29972759.
31. Kelley RK, Verslype C, Cohn AL, et al. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized dis-

continuation study. Ann Oncol. 2017; 28(3): 528–534, doi: 10.1093/annonc/mdw651, indexed in Pubmed: 28426123.
32. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. Clin Cancer Res. 2014; 20(11): 2959–2970, doi: 10.1158/1078-0432.CCR-13-2620, indexed in Pubmed: 24700742.
33. Rankin EB, Giaccia AJ. The receptor tyrosine kinase AXL in cancer progression. Cancers (Basel). 2016; 8(11): E103, doi: 10.3390/cancers8110103, indexed in Pubmed: 27834845.
34. Gerendassh BS, Creel PA. Praktyczne postępowanie w przypadku działań niepożądanych związanych z leczeniem kabozantynibem chorych z rakiem nerkowokomórkowym. Onco Targets and Therapy. 2017; 10: 5053–5064.
35. Heinrich B, Czauderna C, Marquardt JU. Immunotherapy of Hepatocellular Carcinoma. Oncol Res Treat. 2018; 41(5): 292–297, doi: 10.1159/000488916, indexed in Pubmed: 29705790.
36. El-Khoueiry A, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet. 2017; 389(10088): 2492–2502, doi: 10.1016/s0140-6736(17)31046-2.
37. Zhu AX, Finn RS, Edeline J, et al. KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018; 19(7): 940–952, doi: 10.1016/S1470-2045(18)30351-6, indexed in Pubmed: 29875066.
38. Sangro B, Gomez-Martin C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013; 59(1): 81–88, doi: 10.1016/j.jhep.2013.02.022, indexed in Pubmed: 23466307.
39. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391(10126): 1163–1173, doi: 10.1016/S0140-6736(18)30207-1, indexed in Pubmed: 29433850.
40. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003; 228(1): 235–240, doi: 10.1148/radiol.2281020718, indexed in Pubmed: 12759473.
41. Fabregat I. Dysregulation of apoptosis in hepatocellular carcinoma cells. World J Gastroenterol. 2009; 15(5): 513–520, indexed in Pubmed: 19195051.
42. Vogel A., Cervantes A., Chaul et al. Hepatocelular carcinoma : ESMO Clinical Practice Guidelines for diagnossis, treatment and follow-up. Annals of Oncology 2018; 29(supl 4): iv238–iv255.
43. Pazgan-Simon M, Simon K. Problemy diagnostyczne w rozpoznaniu raka pierwotnego wątroby. Hepatologia. 2011.
44. Di Bisceglie AM, Bolondi L, Cheng AL. Cheng A-L. Rak wątrobowokomórkowy. Via Medica. 2010.
45. Forner A, Llovet J, Bruix J. Hepatocellular carcinoma. The Lancet. 2012; 379(9822): 1245–1255, doi: 10.1016/s0140-6736(11)61347-0.
46. Grandhi MS, Kim AK, Ronnekleiv-Kelly SM, et al. Hepatocellular carcinoma: From diagnosis to treatment. Surg Oncol. 2016; 25(2): 74–85, doi: 10.1016/j.suronc.2016.03.002, indexed in Pubmed: 27312032.
47. Knox JJ, Cleary SP, Dawson LA. Localized and systemic approaches to treating hepatocellular carcinoma. J Clin Oncol. 2015; 33(16): 1835–1844, doi: 10.1200/JCO.2014.60.1153, indexed in Pubmed: 25918289.
48. Bupathi M, Kaseb A, Meric-Bernstam F, et al. Hepatocellular carcinoma: Where there is unmet need. Mol Oncol. 2015; 9(8): 1501–1509, doi: 10.1016/j.molonc.2015.06.005, indexed in Pubmed: 26160430.
49. Dufour JF, Hoppe H, Heim MH, et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. Oncologist. 2010; 15(11): 1198–1204, doi: 10.1634/theoncologist.2010-0180, indexed in Pubmed: 21036880.
50. Yada M, Masumoto A, Motomura K, et al. Indicators of sorafenib efficacy in patients with advanced hepatocellular carcinoma. World J Gastroenterol. 2014; 20(35): 12581–12587, doi: 10.3748/wjg.v20.i35.12581, indexed in Pubmed: 25253961.
51. Shao YY, Shau WY, Chan SY, et al. Treatment efficacy differences of sorafenib for advanced hepatocellular carcinoma: a meta-analysis of randomized clinical trials. Oncology. 2015; 88(6): 345–352, doi: 10.1159/000369559, indexed in Pubmed: 25572912.
52. Gbolahan OB, Schacht MA, Beckley EW, et al. Locoregional and systemic therapy for hepatocellular carcinoma. J Gastrointest Oncol. 2017; 8(2): 215–228, doi: 10.21037/jgo.2017.03.13, indexed in Pubmed: 28480062.
53. Murata S, Mine T, Sugihara F, et al. Interventional treatment for unresectable hepatocellular carcinoma. World J Gastroenterol. 2014; 20(37): 13453–13465, doi: 10.3748/wjg.v20.i37.13453, indexed in Pubmed: 25309076.
54. Siu EHL, Chan AWH, Chong CCN, et al. Treatment of advanced hepatocellular carcinoma: immunotherapy from checkpoint blockade to potential of cellular treatment. Transl Gastroenterol Hepatol. 2018; 3: 89, doi: 10.21037/tgh.2018.10.16, indexed in Pubmed: 30603725.
55. Greten T, Sangro B. Targets for immunotherapy of liver cancer. Journal of Hepatology. 2018; 68(1): 157–166, doi: 10.1016/j.jhep.2017.09.007.
56. Llovet J, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016; 2: 16018, doi: 10.1038/nrdp.2016.18.
57. Prieto J, Melero I, Sangro B. Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2015; 12(12): 681–700, doi: 10.1038/nrgastro.2015.173, indexed in Pubmed: 26484443.
58. Greten TF, Ormandy LA, Fikuart A, et al. Immunotherapy of HCC. Rev Recent Clin Trials. 2008; 3(1): 31–39, indexed in Pubmed: 18474013.
59. Brar G, Greten TF, Brown ZJ. Current frontline approaches in the management of hepatocellular carcinoma: the evolving role of immunotherapy. Therap Adv Gastroenterol. 2018; 11: 1–12, doi: 10.1177/1756284818808086, indexed in Pubmed: 30377451.
60. Ikeda M, Morizane C, Ueno M, et al. Chemotherapy for hepatocellular carcinoma: current status and future perspectives. Jpn J Clin Oncol. 2018; 48(2): 103–114, doi: 10.1093/jjco/hyx180, indexed in Pubmed: 29253194.
61. Friedman LS, Keeffe EB. Handbook of liver diseases. 3th Ed. Churchill Livingstone, New York. 2012.

VIA MEDICA

REVIEW ARTICLE

Ewa Wrona[1], Piotr Potemski[1, 2]

[1]The Department of Chemotherapy, Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland
[2]Chemotherapy Clinic, Medical University of Lodz, Poland

A novel immunotherapy — the history of CAR T-cell therapy

Address for correspondence:
Lek. Ewa Wrona
Klinika Chemioterapii Nowotworów
Wojewódzkie Wielospecjalistyczne
Centrum Onkologii i Traumatologii
im. M. Kopernika w Łodzi
ul. Paderewskiego 4, 90–001 Łódź
e-mail: ewawrona00@gmail.com

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 202–207
DOI: 10.5603/OCP.2019.0016

ISSN 2450–1654

ABSTRACT

Robust research over the past 30 years has led recently to the first approval of genetically enhanced T lymphocytes expressing chimeric antigen receptors (CAR T-cells) as a tool to fight cancer. The backbone of the aforementioned therapy is to equip patients' T lymphocytes in a genetically modified receptor that can recognise the antigen present on the surface of a cancer cell with the accuracy of a specific antibody, and to ignite a cytotoxic reaction against it with the function of the T-lymphocyte receptor. Ground-breaking results achieved in patients with haematological malignancies led to multiple clinical trials of CAR T-cell-based therapy in solid tumours. Regardless of the initial hurdles, recent reports suggest that continuous evolution and further improvements of CAR T-cell therapy for solid tumours is as successful as that observed in haematology. Despite the fact that enormous efforts are still to be made, implementation of CAR T-cells into the clinical oncologist's daily routine practice was never as plausible as it is today.

Key words: personalised medicine, genetic modifications, CAR T-cell therapy, solid tumours, haematological malignancies

Oncol Clin Pract 2019; 15, 4: 202–207

Introduction

Over the years, different areas of cancer biology have been explored to find a cure for cancer, the disease with complex, advanced mechanisms that can easily outsmart the best research teams despite their enormous efforts. Only a few studies every year have succeeded to provide a regimen significantly improving the survival of cancer patients. There was an urgency to search other versatile and intelligent approaches for a more effective fight against cancer. The very best field to exploit appeared to be immunotherapy and enhancing the function of patients' own immunological system by equipping its immunocompetent cells with additional functions to independently combat malignant cells.

By altering immunologic response against cancer cells researchers seemed to significantly improve the outcomes in comparison with standard systemic chemotherapy. Immunologic response can be guided in various ways, and the basic studies in that area were rewarded with the Nobel Prize this year, providing a backbone for the discovery of checkpoint inhibitors, e.g. ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab, which have already been successfully implemented into clinical practice. The other approach is directed at increasing the number of tumour infiltrating lymphocytes (TILs), the concentration of which in solid tumours and surrounding stroma is known as a good prognostic factor [1]. The last and the most advanced area of cancer immunotherapy is genetic engineering of patients' immunocompetent cells to produce clones that can act more effectively and accurately, and this area will be discussed in this publication.

The idea of CAR T-cell therapy

Chimeric antigen receptor T-cells (CAR T-cells) are T-lymphocytes genetically modified to express on their surface powerful receptors with enhanced ability to effectively attack cancer cells. Normal T-lymphocytes are unable to fight cancer effectively because they require

major histocompatibility complex (MHC) class I/II antigen recognition to ignite their reaction, and cancer cells deliberately inhibit MHC expression on their surface to be "invisible" to immunocompetent cells. The main concept is to equip patient's T-lymphocytes with additional functionalities to improve recognition, trafficking, and action against cancer cells. Genetic alterations result in creating T-cell receptor (TCR) with an extracellular domain substituted by a fragment of a specific antibody against cancer antigen (scFv). In this way we can combine both of its functions in one chimeric protein: the ability to trigger T-lymphocyte cytotoxic reaction and to recognise with the accuracy of an antibody a chosen antigen on the surface of a malignant cell without the need for MHC class I/II recognition. Additionally, it is known that adding further co-stimulators to CAR protein can prolong T-cell viability and enhance cytotoxic reaction, among other functions [1, 2].

Surprisingly, the very idea of genetically modified receptors on the surface of immunocompetent cells is not recent. The first report on chimeric combination of receptors and antibodies was published in 1989 by Weizmann Institute in Israel [3]. Since then a great amount of effort has been devoted into this area of research, leading to therapeutic success in 2012 when seven-year-old Emily Whitehead was cured from relapsed/refractory B-cell acute lymphoblastic leukaemia (R/R B-ALL) with infusion of anti-CD19 CAR T-cells. CD19 is an example of the ideal antigen for CAR T-cell recognition because it is expressed exceptionally on every B lymphocyte as well as on blast cells that originate from the B-cell line. Her case was a breakthrough not only because she was the first patient with R/R B-ALL, who achieved complete remission after a single course of treatment, but also because she was the very first child enrolled into a clinical study with tisagenlecleucel (Kymriah, Novartis) CAR T-cell therapy. Her case was broadcasted worldwide as an example of this miraculous drug, with headlines playfully reporting the girl cured from cancer by HIV (actually, the HIV virus was used only as a vector in the transduction process) [4]. At the time of writing this manuscript she is still in complete remission advocating in favour of implementing wider access to CAR T-cell therapy.

Manufacturing process

To start to produce CAR T-cells eligible for administration to the patient, a labour-intensive process that requires the cooperation of both clinical and laboratory staff must be undertaken with many carefully performed steps. Firstly, viable T-cells need to be collected from peripheral blood or through leukapheresis. Next, Th17 lymphocytes are filtered and their gross number increased by enforcing T-cell multiplication *ex vivo*. Then a previously prepared viral vector containing genetic information about what the future chimera of the antibody and receptor should look like and what kind of antigen it should recognise transports the information into the infected T-cell. For the transfection process several viruses (especially lentivirus or retrovirus) or plasmids are used. Of course, the viral genome must be altered to silence its own virulence after transfection [5]. As for vector production improvement, a highly accurate and efficient CRISPR/cas9 endonuclease system, as well as a TALEN gene-editing tool, finds their implication, making the production process far more precise and increasing the throughput [6, 7]. The basis of the transfection process is to incorporate the message into the T-lymphocyte genome to enforce expression of numerous functional CARs across its membrane.

Solution of transfected T-cells with high expression of CARs on their surface is further expanded in a cell culture, washed, suspended in a mixture of DMSO/dextran 40/HSA/dextrose/Plasma-Lyte A, and cryopreserved. Sterility tests are conducted before shipping to the facility where it will be administered to the patient [8, 9].

Clinical applications in haematological malignancies

Administration requires premedication with paracetamol and H1-antihistamine. Regarding dosing, there are different ranges of total viable CAR T-cells, which vary between children and adults with numbers between 0.2×10^6 and 6.0×10^8 per kilogram body weight CAR-positive T-cells for Kymriah, and 2×10^6 CAR T-cells per kilogram body weight for Yescarta (trade name for axicabtagene ciloleucel, Gilead, approved for treatment of R/R large B-cell lymphoma). Calculated total number of cells is later infused over three to four doses administered with short breaks one after another [8, 9]. Prior to the infusion the patient must undergo lymphodepleting chemotherapy (fludarabine and cyclophosphamide or equivalent) provided that his/her white blood cell (WBC) count is higher than 1×10^9/L. CAR T-cell infusion must be administered between the second and 14th day after completion of the lymphodepleting chemotherapy [9].

There are many limitations of this treatment. Apart from limited availability of the technology and economic factors, patient specific eligibility criteria must be fulfilled. At the moment of publication FDA registration applies to patients with R/R B-cell ALL and adults with R/R B-cell lymphomas (Table 1). However, efforts are being made to expand those indications for follicular lymphoma (FL) and chronic lymphoblastic leukaemia

Table 1. FDA-approved indications for both tisagenlecleucel and axicabtagene ciloleucel

Generic name	Brand name	FDA approval date	Indications
Tisagenlecleucel	Kymriah, Novartis	August 30, 2017	For patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in second or later relapse [9]
		May 1, 2018	For adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma [9]
Axicabtagene ciloleucel	Yescarta, Gilead	October 18, 2017	For adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma [8]

(CLL). Last but not least, the patient must be able to have his/her lymphocytes harvested, which excludes cases with deep lymphopaenia (less than 300/μL). Viral infections, e.g. HIV, HCV, or HBV, excludes patients from enrolment, as well as active autoimmune disease requiring immunosuppressive therapy. Candidates must also be fit for conditioning chemotherapy with cyclophosphamide and fludarabine or equivalent prior to CAR T-cell infusion with the baseline ECOG performance status of 0–1 [8, 9].

Anticipated adverse events

Unluckily, serious adverse events grade 3 or higher occur in the vast majority of patients treated with Kymriah or Yescarta. Based on the ELIANA and JULIET trials for Kymriah and ZUMA-1 for Yescarta we can assess their incidence as 83% for B-lymphocyte aplasia, 49% for cytokine release syndrome (CRS), 37% for febrile neutropaenia, 22% for hypotension, 18% for hypoxia, 15% for pyrexia, 15% for acute kidney injury, 10% for encephalopathy, and 10% for pulmonary oedema, among others [9].

CRS and neuro toxicities are most life-threatening side effects associated with CAR T-cells infusion. CRS arises from activation of CAR T-cells and death of targeted cells after antigen recognition and TNFα, IL-6 and IFNγ release among others, triggering an avalanche of reactions, which is unlikely to limit itself. The syndrome manifests with fever, hypotension, hypoxia, and tachycardia and can be associated with multiple organ failure and coagulopathy. Severity of CRS is known to correlate with tumour burden. It was observed that fractionation of the infusion volume into 3–4 smaller portions may decrease the risk of CRS. It usually occurs 2–3 days after infusion and lasts for approximately eight days if treated [10].

The majority of neurologic toxicities, e.g. delirium, aphasia, seizures, and encephalopathy, are thought to be reversible; however, the mechanism of central nervous system involvement is not fully understood. Neuro toxicities grade 3 or higher occurred in 31% of patients with median time to onset of four days and median duration of 17 days. There were four deaths related to Yescarta and one to Kymriah reported in the aforementioned studies, all of them due to CRS [8, 9].

One of the natural side effects of CAR T-cell anti-CD19 therapy is B-lymphocyte aplasia. It was proven that some of B-lymphocytes can lack CD19 expression and flee this way from CAR T-cell activity sustaining baseline immunocompetence, although the majority of patients require replacement therapy with intravenous immunoglobulin and prophylactic antibiotics [1, 5]. Aplasia is thought to be a long-lasting side effect that is present at six months after the treatment in 83% of patients (95% CI 69–91%) [11].

Management of side effects

Management of side effects requires standard symptomatic treatment, although for CRS and neuro-toxicities grade 2 or higher, administration of tocilizumab alone or with corticosteroids is recommended as well [8, 9]. Tocilizumab is an immunosuppressive drug inhibiting specifically IL-6, widely available in Poland in the therapy of rheumatoid arthritis (RoActemra, Roche). The US Food and Drug Administration (FDA) approved tocilizumab for treatment of CRS triggered by CAR T-cell therapy. It is suggested the administration of 8 mg/kg intravenously over one hour repeating every eight hours if needed. A maximum of three doses in a 24-hour period can be administered with a total of four doses [8, 9]. If there is no improvement within 24 hours after starting tocilizumab, administration of corticosteroids as well, preferably methylprednisolone 1 mg/kg intravenously twice a day or dexamethasone 10 mg every six hours, is recvommended [8, 9].

Clinical trials

Based on clinical trial data that led to Yescarta and Kymriah FDA approval for adults with R/R B-cell lymphoma (ZUMA-1 and JULIET study), we acknowledge the progression-free survival (PFS) rate at 15 months to be 41% (95% CI 31–50), median duration of response to be 11.1 months (95% CI 3.9 to could not be estimated), the median PFS to be 5.8 months (95% CI 3.3 to could not be estimated), and OS rates of 52% at 18 months with median overall survival (OS) not reached (95% CI 12.0 months to could not be estimated) [12].

For Kymriah, in the ELIANA study of 75 patients not older than 21 years with R/R B-cell ALL the overall remission rate within three months was 81%, the rates of event-free survival and OS were 73% (95% CI 60–82) and 90% (95% CI 81–95), respectively, at six months and 50% (95% CI 35–64) and 76% (95% CI 63–86) at 12 months of follow-up [11].

Worth mentioning is the third, still ongoing, trial — TRANSCEND NHL-001 in R/R aggressive non-Hodgkin lymphomas (DLBCL, CLL, MZL, PMBCL, FL) with lisocabtagene maraleucel (liso-cel, Celgene). It reported an overall response rate (ORR) of 74%, and complete remission (CR) of 52% with only 1% and 15% of grade 3 or higher CRS and neuro toxicity, respectively, which seems to be highly promising compared with the data on Kymriah and Yercarta [13]. The other study of interest described the efficacy of CAR T-cells targeting B-cell maturation antigen (BCMA) expressed highly on multiple myeloma malignant cells. Twenty-one patents were reported to be treated with bb2121 (anti-BCMA CAR T-cells), with an ORR of 89% and follow-up ranging from 1.4 to 54.4 weeks, with only one progression among 21 heavily pre-treated patients [14].

Availability

Although CAR T-cell therapy is undoubtedly highly effective, it is not available outside clinical trials and private health care system. The majority of clinical trials are carried on at facilities in China and in the USA, with the University of Pennsylvania being the leading one. In Europe, the only institutions having some experience with CAR T-cell clinical trials are in the Netherlands and in the UK [1, 15].

Due to cost concerns the UK's NHS initially rejected in August 2018 broad access to Gilead's Yescarta, although the application sparked further discussion. Finally, late September 2018 brought an agreement that resulted in the founding by the NHS of a treatment programme with Yescarta for 200 adult patients with R/R large B-cell lymphoma a year and with Kymriah for 30 R/R B-ALL children and young adults a year. This precedence makes the UK the first country in Europe offering, still to a limited number of patients, these novel and highly promising therapies.

Apart from clinical trials, several institutions offer private access to CAR T-cell therapy with costs fully covered by patients, with Israel and the USA being the leading ones. Yescarta and Kymriah cost $373,000 and $475,000, respectively. An NHS report last year, which summarised costs of treatment with Yescarta jointly with costs of conditioning therapy, hospitalisation, adverse event management, and follow-up, estimated the total cost at £583,362 compared with £80,106 for standard of care [16]. However, contrasting opinions seem to appear recently in peer-reviewed journals assessing life-years gained and quality-adjusted life-years (QALYs) gained in favour of Kymriah vs. standard care. In cases of childhood R/R B-ALL, 40% of patients treated with Kymriah are expected to be long-term survivors with life-years gained of 10.34 years and 9.28 QALYs gained *vs*. 2.43 years and 2.10 QALYs gained for clofarabine treatment, in comparison. These enormous differences result in a cumulative cost-effectiveness ratio of $46,000 per QALY gained between Kymriah and clofarabine [17].

Potential in solid tumours

Translation of CAR T-cell success in haematology into the treatment of solid tumours is highly challenging due to many features of solid tumours that in haematological malignancies are minor obstacles. Using genetically modified lymphocytes to combat blasts that share haematopoietic origin and have the potential to migrate through the same locations, like blood, bone marrow, or lymph nodes, might contribute to anti-CD19 CAR T-cell therapy success. Due to genetic instability (somatic mutations) and heterogeneity, cancer cells have variable antigen expression levels on the surface of the cell between subclones of cancer cells. Additionally, antigens expressed by solid tumours are not exclusive comparing with healthy cells, being the foundation of serious "on-target off-tumour" side effects that limit its application [5]. Choosing an ideal tumour antigen (present on every malignant cell and not expressed on the surface of healthy ones) to be targeted by CAR T-cells seems to be the biggest obstacle. Many candidate antigens were under the scope, e.g. MUC1 [18, 19], HER2 [20], G2D [2], CEA [5], EGFR [5], GP100 [21], and mesothelin [2] among many others [22]. As an example, prostate-specific membrane antigen (PSMA) seems to be the perfect target, because preliminary data report it can be found on malignant prostate cells and the endothelium of some tumour vasculature, but it is not expressed by normal cells [2].

The other obstacles are immunosuppressive properties of surrounding stroma that mute activation of the immune system. Sadly, T-cells do not infiltrate tumour tissue easily, and efforts are being made to implement additional receptors and co-stimulators into the CAR T-cell membrane to simplify its trafficking, as well as altering the chemokine secretion profile of the CAR T-cell to correlate with the cancer cells [2, 7]. Surprisingly, the addition of anti-PD-1 antibody appeared to decrease the myeloid-derived suppressor cell (MDSC) population in the tumour stroma, and it augments the response rate through increased CAR T-cell anti-tumour activity [5, 23].

Case series

Sadly, there are only a few case reports and trials on CAR T-cell in solid tumours. There are publications reporting CAR T-cell usage in patients diagnosed with malignant pleural mesothelioma [18], pancreatic ductal adenocarcinoma [18], colorectal adenocarcinoma [2, 24], prostate cancer [2], breast cancer [25], melanoma [21], or osteosarcoma [20] among others. The majority of authors report poor outcomes of the treatment with rare and short-lasting ORR and occasional CR, mostly in melanoma cases [21]. A large number of clinical trials are still recruiting, and more data on clinical effectiveness of CAR T-cell therapy in solid tumours are to be anticipated in near future.

A ground-breaking case report of a female patient with chemorefractory metastatic breast cancer achieving CR after infusion of genetically modified T lymphocytes at the National Cancer Institute in Bethesda, USA was published in June 2018. Interestingly, researchers created a suspension of four different T-cell clones directed against the four highest expressed antigens on the surface of the patient's cancer cells. After myeloablation therapy and infusion of modified autologous T-lymphocytes she continued pembrolizumab as a maintenance therapy and achieved CR after a year of treatment, and sustained it for 22 months of follow-up [25].

New ideas

Because CAR T-cell therapy, apart from its ground-breaking effectiveness, has some serious flaws, efforts are being made to alternate the original idea in order to overcome its limitations, e.g. serious and common side effects, robust manufacturing process, high costs. Studies are ongoing in both the public and private sector exploring different approaches to reach improvement.

Using natural killer (NK) lymphocytes instead of T-lymphocytes for gene editing emerged as one of the major initiatives. The main advantage brought by the use of NK lymphocytes is that they ignite their activity regardless of human leukocyte antigen (HLA) matching and for that reason do not need to be harvested from a patient or HLA-matched donor. This distinctive feature makes CAR NK cell-based therapy an "off-the-shelf" resource for cancer therapy in contrast with CAR T-cells, which are highly personalised and produced specifically "for-the-patient".

The concept of creating CARs on the surface of NK-lymphocyte is not entirely new. NK-lymphocytes obtained from pooled peripheral or cord blood, as well as from cell line NK92, were previously genetically altered. In the case of NK92 cell line, to prevent permanent engraftment of NK92 cells harvested initially from a non-Hodgkin lymphoma patient, altered lymphocytes needed to be additionally irradiated, but the procedure lowered significantly their viability and ability to proliferate *in vivo* [26]. For all the aforementioned sources of NK-lymphocytes production process had comparable efficiency as in the case of T-lymphocytes, and, additionally, infusions appeared to be much safer with rare side effects at much lower grades of intensity. Despite having lower toxicity, this therapy, surprisingly, turned out to be ineffective with negligible ORR rates [27].

However, a recent study published data on genetically modified NK-lymphocytes obtained through transduction of genetic information on CARs into immunologically pluripotent stem cells (iPSC) that were afterwards forced to transform into NK lymphocytes expressing CAR. The process was described as extremely efficient with a high count of viable CAR NK-cells harvested. Ovarian cancer mice models were then infused with suspension of CAR NK-cells, among others, for comparison showing substantial and long-lasting regression of the tumour volume, proving its superiority above modified CAR T-cell therapy in this case [28].

CAR T cells are forced to express modified CAR particles among endogenous T-cell lymphocyte receptors (TCR), receptors that are recognised as patient specific, and that is the main reason restricting it from being used in an "off-the-shelf" manner. Another example of an approach to overcome this obstacle is to genetically silence expression of native TCR on CAR T-cells that could be given regardless of HLA compatibility with no risk of triggering graft vs. host disease. Several companies made efforts in this area of research, as well as equipping CAR T-cells in suicide genes or other co-stimulatory particles that could add improvements if needed [2, 29]. Apart from large pharmaceutical companies, biotechnology businesses like Cellectis, Parker Institute for Cancer Immunotherapy, or TMunity and others spread over the UK, Australia, China, or Singapore could be the best examples of attempts to commercialise CAR T-cell therapies through the aforementioned improvements.

Conclusions

CAR T-cell therapy is considered highly innovative and effective, undoubtedly being the biggest breakthrough in cancer treatment in years. However, clinical oncologists need to be aware not only of the obvious virtues of this approach but also its limitations. However, the race to create a cancer cure has not been won yet, and countless research teams are working on the idea of training lymphocytes to highly specifically, safel, and more efficiently deal with cancer cells, which will hopefully evolve into an "off-the-shelf" treatment with a more affordable price for caregivers.

Regardless of further improvements, we should all be prepared for the implementation of therapy with genetically modified lymphocytes in the future. Most importantly, nowadays we also should be able to answer patients' questions on this breakthrough treatment and inform them about its advantages and disadvantages. Furthermore, we should all be aware of the possible side effects and its management, to be prepared for the moment when we can treat our patients with CAR T-cell therapies.

References

1. June C, O'Connor R, Kawalekar O, et al. CAR T cell immunotherapy for human cancer. Science. 2018; 359(6382): 1361–1365, doi: 10.1126/science.aar6711.
2. Yong C, Dardalhon V, Devaud C, et al. CAR T-cell therapy of solid tumors. Immunology and Cell Biology. 2017; 95(4): 356–363, doi: 10.1038/icb.2016.128.
3. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A. 1989; 86(24): 10024–10028, doi:10.1073/pnas.86.24.10024, indexed in Pubmed: 2513569.
4. Allen N. Emily Whitehead: girl whose cancer was 'cured' by HIV. 2012. https://www.telegraph.co.uk/news/worldnews/northamerica/usa/9738355/Emily-Whitehead-girl-whose-cancer-was-cured-by-HIV.html.
5. Androulla M, Lefkothea P. CAR T-cell Therapy: A New Era in Cancer Immunotherapy. Current Pharmaceutical Biotechnology. 2018; 19(1): 5–18, doi: 10.2174/1389201019666180418095526.
6. Levine BL, Miskin J, Wonnacott K, et al. Global Manufacturing of CAR T Cell Therapy. Mol Ther Methods Clin Dev. 2017; 4: 92–101, doi: 10.1016/j.omtm.2016.12.006, indexed in Pubmed: 28344995.
7. Qasim W, Zhan H, Samarasinghe S, et al. Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells. Sci Transl Med. 2017; 9(374): 1–9, doi: 10.1126/scitranslmed.aaj2013, indexed in Pubmed: 28123068.
8. FDA. Full prescribing information: axicabtagene ciloleucel. 2017. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.
9. FDA. Full prescribing information: tisagenlecleucel. 2017. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.
10. Maude S, Frey N, Shaw P, et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. New England Journal of Medicine. 2014; 371(16): 1507–1517, doi: 10.1056/nejmoa1407222.
11. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018; 378(5): 439–448, doi: 10.1056/NEJMoa1709866, indexed in Pubmed: 29385370.
12. Neelapu S, Locke F, Bartlett N, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. New England Journal of Medicine. 2017; 377(26): 2531–2544, doi: 10.1056/nejmoa1707447.
13. Abramson JS, Palomba L, Gordon LI, et al. Transcend NHL 001: Immunotherapy with the CD19-Directed CAR T-Cell Product JCAR017 Results in High Complete Response Rates in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma. Blood 2016; 128(22): 4192 LP-4192. http://www bloodjournal org/content/128/22/4192. abstract.
14. Berdeja JG, Lin Y, Raje N, et al. Durable Clinical Responses in Heavily Pretreated Patients with Relapsed/Refractory Multiple Myeloma: Updated Results from a Multicenter Study of bb2121 Anti-Bcma CAR T Cell Therapy. Blood 2017; 130(Suppl 1):740 LP-740. http://www bloodjournal org/content/130/Suppl_1/740. abstract.
15. Maher J. Immunotherapy of Malignant Disease Using Chimeric Antigen Receptor Engrafted T Cells. ISRN Oncology. 2012; 2012: 1–23, doi: 10.5402/2012/278093.
16. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess. 2017; 21(7): 1–204, doi: 10.3310/hta21070, indexed in Pubmed: 28244858.
17. Whittington M, McQueen R, Ollendorf D, et al. Long-term Survival and Value of Chimeric Antigen Receptor T-Cell Therapy for Pediatric Patients With Relapsed or Refractory Leukemia. JAMA Pediatrics. 2018; 172(12): 1161, doi: 10.1001/jamapediatrics.2018.2530.
18. Beatty GL, Haas AR, Maus MV, et al. Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce anti-tumor activity in solid malignancies. Cancer Immunol Res. 2014; 2(2): 112–120, doi: 10.1158/2326-6066.CIR-13-0170, indexed in Pubmed: 24579088.
19. You F, Jiang L, Zhang B, et al. Phase 1 clinical trial demonstrated that MUC1 positive metastatic seminal vesicle cancer can be effectively eradicated by modified Anti-MUC1 chimeric antigen receptor transduced T cells. Sci China Life Sci. 2016; 59(4): 386–397, doi: 10.1007/s11427-016-5024-7, indexed in Pubmed: 26961900.
20. Ahmed N, Brawley VS, Hegde M, et al. Human Epidermal Growth Factor Receptor 2 (HER2) -Specific Chimeric Antigen Receptor-Modified T Cells for the Immunotherapy of HER2-Positive Sarcoma. J Clin Oncol. 2015; 33(15): 1688–1696, doi: 10.1200/JCO.2014.58.0225, indexed in Pubmed: 25800760.
21. Sharpe M, Mount N. Genetically modified T cells in cancer therapy: opportunities and challenges. Disease Models & Mechanisms. 2015; 8(4): 337–350, doi: 10.1242/dmm.018036.
22. Kakarla S, Gottschalk S. CAR T Cells for Solid Tumors: Armed and Ready to Go? Cancer J. 2014; 20(2): 151–155, doi: 10.1097/ppo.0000000000000032.
23. Chen N, Morello A, Tano Z, et al. CAR T-cell intrinsic PD-1 checkpoint blockade: A two-in-one approach for solid tumor immunotherapy. OncoImmunology. 2017; 6(2): e1273302, doi: 10.1080/2162402x.2016.1273302.
24. Zhang C, Wang Z, Yang Z, et al. Phase I Escalating-Dose Trial of CAR-T Therapy Targeting CEA Metastatic Colorectal Cancers. Mol Ther. 2017; 25(5): 1248–1258, doi: 10.1016/j.ymthe.2017.03.010, indexed in Pubmed: 28366766.
25. Zacharakis N, Chinnasamy H, Black M, et al. Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer. Nat Med. 2018; 24(6): 724–730, doi: 10.1038/s41591-018-0040-8, indexed in Pubmed: 29867227.
26. Zhang C, Oberoi P, Oelsner S, et al. Chimeric Antigen Receptor-Engineered NK-92 Cells: An Off-the-Shelf Cellular Therapeutic for Targeted Elimination of Cancer Cells and Induction of Protective Antitumor Immunity. Front Immunol. 2017; 8: 533, doi: 10.3389/fimmu.2017.00533, indexed in Pubmed: 28572802.
27. Tang X, Yang L, Li Z, et al. First-in-man clinical trial of CAR NK-92 cells: safety test of CD33-CAR NK-92 cells in patients with relapsed and refractory acute myeloid leukemia. Am J Cancer Res. 2018; 8(6): 1083–1089, indexed in Pubmed: 30034945.
28. Li Ye, Hermanson D, Moriarity B, et al. Human iPSC-Derived Natural Killer Cells Engineered with Chimeric Antigen Receptors Enhance Anti-tumor Activity. Cell Stem Cell. 2018; 23(2): 181–192.e5, doi: 10.1016/j.stem.2018.06.002.
29. Ruella M, Kenderian SS. Next-Generation Chimeric Antigen Receptor T-Cell Therapy: Going off the Shelf. BioDrugs. 2017; 31(6): 473–481, doi: 10.1007/s40259-017-0247-0, indexed in Pubmed: 29143249.

VIA MEDICA

REVIEW ARTICLE

Dariusz Pysz-Waberski[1], Weronika Bulska-Będkowska[2], Ewa Wachuła[3]

[1]Clinical Oncology Department, University Clinical Centre in Katowice, Poland
[2]Department and Clinic of Internal Diseases and Oncology Chemotherapy, Faculty of Medicine in Katowice, Medical University of Silesia in Katowice, Poland
[3]Oncology Clinic, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Poland

Treatment of chronic pain in oncology: cooperation between the oncologist and psychooncologist

Address for correspondence:
Lek. Ewa Wachuła
Klinika Onkologii, Wydział Lekarski
z Oddziałem Lekarsko-Dentystycznym
w Zabrzu
Śląski Uniwersytet Medyczny w Katowicach
e-mail: e.wachula@wp.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 208–216
DOI: 10.5603/OCP.2019.0027
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

The aim of this work is to present the problem of chronic pain in neoplastic disease as a situation requiring diagnosis and interdisciplinary treatment. The phenomenon of chronic pain, its types, and causes are discussed. A discussion was held on appropriate scales for measuring pain intensity. Pharmacotherapy and psychotherapy were primarily presented among the discussed treatment methods, and issues related to other methods of interactions related to the treatment of patients with chronic pain in the course of neoplastic disease were discussed. The key aspect of the article is to draw attention to the implementation of multi-specialist treatment of chronic pain, including personalised solutions and the accommodation of the most favourable form of therapy and the methods of its implementation.

Key words: chronic pain, pain treatment, pharmacotherapy, psychotherapy, oncology, psychooncology

Oncol Clin Pract 2019; 15, 4: 208–216

Introduction

The incidence of cancer is constantly growing both in the world and in Poland. Malignant neoplasms are the second cause of death in Poland after cardiovascular disease. It is estimated that one in four people will die from cancer [1]. In more than half of patients cancer is in an advanced stage at the time of diagnosis and is associated with the presence of clinical symptoms.

In addition to anti-cancer therapy the proper diagnostics and treatment of pain is one of the key aspects of oncological care.

Literature data show that during radical treatment, as many as 30–50% of patients experience pain, and in advanced stages this problem affects over 80% of patients [2].

Pain should be considered as a psychosomatic phenomenon, which is defined as a subjective, multi-area experience that is individually felt by the person. According to the International Association for the Study of Pain (IAPS) and the World Health Organisation (WHO), pain is "an unpleasant sensory and emotional sensation caused by actual or potential tissue damage". This definition includes sensory (related to pain perception) as well as emotional components (related to mental reactions to a given painful stimulus). The emotional component is subjective and, as mentioned earlier, it has an individual dimension for a given patient [3, 4].

The following factors characterise pain as a holistic experience:

— physiological symptoms of pain (physical dimension);
— the impact of pain on the patient's functioning and self-care activities (functional dimension);
— the impact of pain on emotions as well as the quantity and quality of social relations (the psychosocial dimension);
— understanding the meaning of suffering, purpose of life, worldview, life attitudes (spiritual dimension);

— history of pain experiences, current experience of pain, anxiety problems, adaptation to cancer (behavioural dimension) [4].

Pain is a manifestation of cancer, occurring at various stages of disease, starting from being the first symptom of the developing disease (primary tumour or metastases), pain occurring during anti-cancer treatment (oncological surgery, chemotherapy, radiotherapy, and others), up to pain at the end-stage of the disease. Pain can also occur during remission or in cured patients as a consequence of previous causal treatment [5, 6]. The results of a meta-analysis conducted in 2016 and based on the data from over 66,000 people showed that 39.3% of people experienced pain associated with the treatment, 55% suffered from pain during cancer treatment, and 66.4% suffered from pain in the advanced, metastatic, or terminal phase of the disease [7]. Scientific analyses performed in the last two decades suggest an improvement in the pharmacological adequacy of analgesic therapy. However, almost 30% of patients still do not receive analgesics adequately to the intensity of pain [8].

In the current, 11th version of the International Classification of Diseases (ICD), chronic pain is defined as persistent (continuous) or recurrent (intermittent, episodic) for more than three to six months. It does not play the role of warning physiological nociception in acute conditions. It is estimated that chronic pain affects about 20% of people worldwide [6]. In response to this issue, new categories of chronic have pain emerged, including:
— chronic primary pain;
— chronic cancer pain;
— chronic post-traumatic and post-operative pain;
— chronic neuropathic pain;
— chronic headache and mouth and facial pain;
— chronic visceral pain;
— chronic musculoskeletal pain [6].

Types and causes of cancer pain

The Polish Society for the Study of Pain (PTBB) classifies pain in cancer according to the cause and distinguishes the following types of pain:
— pain caused by the presence of primary tumour/metastases;
— pain caused by the diagnosis and treatment of cancer;
— pain syndromes indirectly related to cancer or not related to oncological disease;
— breakthrough pain [9].

In turn, the European Society for Clinical Oncology (ESMO), among the causes of non-tumour-related pain, additionally distinguished pain occurring in convalescents [10].

Cancer pain can also be categorised by the type of ailments: neuropathic pain (non-receptor, pathological) and nociceptive pain (receptor), which consists of somatic and/or visceral pain [10].

Pain caused by the presence of a tumour

The pain caused by the presence of the tumour is usually mixed and consists of several types of pain with different pathomechanisms (i.e. neuropathic, somatic, and visceral).

Somatic pain affects 70–80% of patients with existing tumour mass and it may be the result of irritation of nerve endings (nociceptors) or lowering their excitability threshold in the case of inflammation around tumour tissues and consequent release of inflammatory mediators (e.g. prostaglandins, histamine, bradykinin) [11, 12]. Somatic pain derives from bones, joints, muscles, skin, or connective tissue. Pain from soft tissues is the result of occlusion of blood and/or lymph vessels by the tumour and infiltration of soft tissues and serous membranes. On the other hand, bone pain arises from the invasion of the bone marrow by the tumour, which leads to an increase in intraosseous pressure, periosteal distension, and proliferation of nerve fibres in the bone marrow and periosteum as a consequence of nerve growth factor (NGF) activity. Metastases in the bones can cause local or root pain [9]. Somatic pain is acute pain, strictly located, which increases in direct proportion to the deterioration of the local condition [13].

Visceral pain caused by the presence of a tumour occurs in 30% of patients [11]. It is described by patients as aching, colic, and diffuse pain. Visceral pain arises in the organs of the digestive system due to stretching of the organ's capsule, compression or pulling through the tumour tissue of ligaments, blood vessels, mesentery, pleura, or peritoneum. Inflammatory mediators, as in the pathomechanism of somatic pain, can stimulate visceral nociceptors. In addition, infiltration of nerve fibres and vessels that supply visceral organs is responsible for the development of diffuse pain [9, 11].

Neuropathic pain due to tumour expansion occurs in 30–40% of patients and shows paroxysmal and stabbing features [11]. It is accompanied by breakthrough pain, that is short and very strong. It can also be characterised by generalised dysaesthesia, hyperalgesia, and allodynia. Depending on primary tumour or metastases location neuropathic pain is divided into peripheral or central. Neuropathic pain is the result of pressure or damage of peripheral nerves or nerve plexuses. Peripheral nerve injury is a signal for the parent's neuron body in the spinal ganglia to activate gene expression and production of protein particles transported to the site of injury. As a result of biochemical changes, new receptors are formed, which are the source of stimuli responsible for the formation of paroxysmal pain. In addition, nerve damage leads to pathological synaptic connections between different types of nerve fibres, contributing to the incorrect sensation of stimuli (analogous to allodynia, hy-

peralgesia, dysaesthesia) [12]. In addition, neuropathic pain occurs in paraneoplastic syndromes (e.g. peripheral sensory polyneuropathy, Lambert-Eaton myasthenic syndrome [LEMS], paraneoplastic myopathy, cerebellar degeneration, paraneoplastic encephalitis) [9].

Pain caused by diagnostics and anticancer treatment

Approximately 20% of cancer patients experience iatrogenic pain caused by chemotherapy, radiotherapy, hormone therapy, corticosteroid therapy, targeted therapy, or surgery [9–11]. Iatrogenic pain is usually neuropathic in nature because it is the result of nerve damage, leading to defective perception of pain in the peripheral or central nervous system [13].

Peripheral neuropathies are most often caused by the use of anti-cancer neurotoxic drugs (vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, platinum derivatives). Neuropathic pain after cytotoxic drugs is often described by patients as tingling, numbness, stinging, or stabbing pain. During hormone therapy with antioestrogens and aromatase inhibitors, side effects may appear in the form of osteoarticular pain [10].

Granulocyte colony-stimulating factors (G-CSF) most commonly induce bone pain during chemotherapy [9]. However, as a result of high doses of corticosteroids in premedication for chemotherapy or symptomatic treatment during palliative care, there is a risk of developing painful inflammatory changes of the skin and oral mucosa, infection, peripheral neuropathy, sterile osteonecrosis (Calve's, Legg's, and Perthes' disease), osteoporosis, and osteonecrosis [9, 10, 13].

Surgical procedures may result in damage of the peripheral nerves and consequently persistent pain after mastectomy, thoracotomy, phantom pain, stump pain. In turn, radiotherapy can lead to fibrosis of the brachial or lumbar plexuses, myelopathy, and radiation-induced necrosis. In addition, radiotherapy is responsible for the occurrence of chronic inflammation of the mucous membranes of the mouth, throat, oesophagus, intestines, and anus [9, 10].

In addition to pain of iatrogenic origin, there are also — often overlooked — pain complaints associated with the diagnosis and invasive procedures, developed by the ESMO classification of non-tumour-related pain, distinct categories for iatrogenic pain and severe procedural pain. Acute pain syndrome may be a complication after puncture, biopsy, endoscopy, angiography, and other diagnostic interventions [10].

Pain in convalescents is another, separate category of pain symptoms defined by the ESMO. It may be a consequence of procedures performed as part of observation or persistent side effects of the therapies used [10].

An example of a group of patients particularly exposed to persistent iatrogenic pain are women after radical surgical treatment due to breast cancer and supplementary chemotherapy with paclitaxel and radiotherapy to the chest wall area.

Other pain syndromes in cancer patients

The category of other pain syndromes most often concerns ailments unrelated to cancer and anticancer treatment (e.g. diabetic neuropathy, fibromyalgia, angina pectoris, tension and migraine headaches, osteoarthritis, *Herpes* virus infection and subsequent postherpetic neuralgia, acute thrombotic syndromes, immobilisation leading to activation of trigger points and myofascial complaints, and others). The used anti-cancer treatment may in these situations deepen the pre-existing pain [9, 10].

Breakthrough pain

Breakthrough pain is an episodic and transient exacerbation of pain in patients successfully treated with opioids due to cancer pain. The Polish Society for the Study of Pain (PTBB) divides pain into three categories:

— spontaneous pain caused by unknown aetiological factors;
— incidental pain, which may be voluntary (e.g. when attempting to move) or involuntary (e.g. colic pain);
— procedural pain that arises during care, diagnostic, or rehabilitation procedures [9].

Breakthrough pain, regardless of the cause, is characterised by a rapid increase in the severity of pain (on average up to 10 min) and short duration (up to about 50 min).

Pain assessment

An inseparable element of effective analgesia is clinical pain assessment, including the location, migration, nature (quality), intensity, and mitigating factors, pain intensity, efficacy and tolerance of previous treatment, and the occurrence of breakthrough pain. These factors allow us to determine the pathomechanism (type) of pain. An important element of pain assessment is also the evaluation of the mental component [9].

The use of appropriate analgesia should be preceded by an accurate interview and assessment of pain, using formal, validated assessment tools. Due to the complexity of the nature of cancer pain and attempts to classify it, no uniform, universally binding classification of cancer pain has been determined [2].

The most popular and useful tool recommended for the assessment of pain intensity is the NRS (Numerical Rating Scale). It is a 10-point numerical scale in which 0 means no pain, 1–3 (up to 4) means mild pain, 4–6 (up to 7) moderate pain, 7–8 strong pain, and 9–10 very strong pain. The patient evaluates the pain intensity by indicating the number characterising his/her pain sensation. This scale is a standardised tool and is used not only to assess the intensity of pain, but also the effectiveness of treatment. Effective analgesic treatment is when the severity of pain measured by the NRS scale is ≤ 3 [2, 9].

Another method enabling descriptive assessment of pain intensity is the Verbal Rating Scale (VRS), available in two versions, i.e. either four-stage: no pain, weak, moderate, and severe pain, or five-stage Likert version: no pain, weak, moderate, strong, and unbearable pain [2].

The NRS (numerical) scale is more sensitive in comparison to the VRS (verbal) scale; hence, its use in clinical practice and scientific analyses is recommended [9, 14].

Among the available pain assessment tools, there are also image scales (e.g. with facial expressions defining the current state and dedicated mainly to children and people with impaired contact). The next scale is the PHHPS (Prince Henry Hospital Pain Score) used to assess the severity of pain at rest and during movement. It is used in people with postoperative pain [14].

The exact assessment of pain should not be based solely on the evaluation of its intensity but should also include a qualitative assessment of pain and its impact on the patient's functioning. For this purpose, the Brief Pain Inventory (Short Form), the Pain Assessment Sheet, the McGill Pain Questionnaire, and the Doloplus scale are used. In some patients, the test should include an additional assessment of touch, pricking, pressure, temperature difference, vibration, and time summation. This mainly applies to patients with a neuropathic component of pain. Throughout the treatment period, it is necessary to constantly monitor analgesia and vital signs. In recent years, different new forms of screening tools have been developed to facilitate the diagnosis of neuropathic pain, clarify its character, and implement appropriate treatment. It is emphasised that a reliable measurement of pain intensity should be based on more than one method [16]. An example of additional methods may be the DN4 questionnaire (Douleur Neuropathique 4 Questions), PainDETECT Questionnaire, LANSS (Leeds Assessment of Neuropathic Symptoms and Sings), or NPQ (Neuropathic Pain Questionnaire). On the basis of the Delphi analysis, the use of the DN4 scale is particularly recommended for the assessment of neuropathic pain [9, 15].

To assess the severity of pain and its control, it may be useful to propose to the patient that they keep a so-called diary of pain. The patient can use different forms of expressing his/her feelings written in the table or in another way (e.g. by using a verbal description or marking on a scale from 1 to 10 an appropriate number defining his/her pain sensation or drawing a face symbolising the appropriate level of pain sensations). The table can also have an extended version, in which the patient records all information about taken medicines (date, time, medicine, its effectiveness, and others). The mentioned form may additionally support the diagnostic and therapeutic process [17].

Psychological reactions to pain

It is well recognised that pain is perceived in the physical (somatic) mental, social, and spiritual dimensions. The pain caused by cancer, regardless of its stage, has a negative impact on the patient's quality of life, and a low quality of life contributes to an increase of sensitivity to pain and reduces tolerance to pain. Chronic pain, due to its long duration, contributes to the reduction of physical, professional, and social activity [4].

The deterioration of the quality of life of people with chronic pain is also affected by physiological, psychological, and social disorders. This is not directly related to the aetiology of pain, but closely correlates with the duration and intensity of pain. Chronic pain consequently prevents people from carrying out professional tasks, contributes to the limitation and weakening of social contacts, and even worsening of functioning in life roles. Patients develop a sense of hopelessness and negative emotional states, which may result in depression and anxiety [4]. It was found that in the course of cancer the risk of mood and anxiety disorders increases, affecting 47% of cancer patients. The most frequently diagnosed include the following: adaptive (32%), depressive (6%), and isolated anxiety disorders (2%) [2].

Treatment of pain

Pharmacotherapy

Pharmacological treatment of cancer pain is based on WHO recommendations according to the so-called three-stage analgesic ladder.

The first stage of the analgesic ladder

Stage I drugs include non-opioid analgesics for low-intensity pain (1–4 on the NRS scale according to PTBB) and bone pain [9, 10]. This group includes NSAIDs, paracetamol, and metamizole. Paracetamol is safer than NSAIDs and it is recommended by PTBB

as the first choice analgesic in low-intensity pain [9]. In cancer pain with an inflammatory component (including bone pain), NSAIDs are recommended [9, 10]. In addition, non-opioid analgesics may also be used in breakthrough pain in some situations [9]. If the cause of neuropathic pain is nerve compression without permanent damage to the nervous tissue, anti-inflammatory drugs can be beneficial. In the case of permanent nerve damage, NSAIDs are ineffective [18].

As a result of intensive treatment, side effects characteristic for individual groups can occur. Each side effect increases the suffering of cancer patients and worsens the quality of life. Side effects of NSAIDs include the following: gastric mucosa damage, gastrointestinal bleeding, as well as liver and kidney damage. Special care should be taken in elderly people due to the severity of heart and kidney failure. In addition, NSAIDs increase the risk of myocardial infarction and ischaemic stroke, even if used within a short period of time [17]. Metamizole used in colic and breakthrough pain can cause bone marrow damage. An overdose of paracetamol may result in liver damage [13].

The second stage of the analgesic ladder

Drugs of the second stage of the analgesic ladder are so-called weak opioids, used for moderate pain (4–6 on the NRS scale according to PTBB). This group includes tramadol, codeine, and dihydrocodeine [9, 10]. They are used in the case of ineffectiveness of drugs of the first level of the WHO analgesic ladder. Weak opioids are characterised by a ceiling effect — exceeding the maximum dose does not increase analgesia, but only increases the risk of side effects [18]. Tramadol is the recommended first-choice drug of the second stage of the analgesic ladder [9]. It should be remembered, however, that the analgesic activity of tramadol is dependent on the CYP2D6 enzyme; therefore, in people not metabolising the substrates of this enzyme, the analgesic effect is weaker. In addition, care should be taken in the elderly and in patients with epileptic seizures, because tramadol decreases the seizure threshold. It should not be used concomitantly with antidepressants due to the risk of serotonergic syndrome [9, 10].

Opioids have an additional antitussive and antidiarrhoeal effect, reducing the severity of additional symptoms of cancer [13]. Codeine and dihydrocodeine can be used in patients with pain of moderate intensity accompanied by cough. It should be remembered that codeine induces severe side effects (especially in young people) and is not the preferred drug according to PTBB recommendations [9]. In the case of long-term use of opioid drugs, some patients may experience persistent constipation and nausea and vomiting. When starting opioid use, antiemetics should be recommended for the first 5–7 days and laxatives [9].

On the second stage of the analgesic ladder the small doses of the so-called strong opioids (i.e. morphine 30 mg orally daily, oxycodone 20 mg orally daily, hydromorphone 4 mg orally daily) can be also used [9]. There is no evidence of increased side effects of this treatment regimen compared to the use of so-called weak opioids [10].

According to PTBB and ESMO recommendations, weak and strong opioids should not be combined [9, 10].

The third stage of the analgesic ladder

Drugs of the third stage (so-called strong opioids — e.g. fentanyl, morphine, tapentadol, oxycodone, hydromorphone, buprenorphine, methadone) are used in the case of ineffectiveness of drugs from previous groups. Morphine, oxycodone, hydromorphone should be the first-line drugs for the treatment of moderate to severe pain (6–10 on the NRS scale) [9, 10].

In addition to the analgetic effect morphine also reduces the feeling of dyspnea. The advantages of morphine in the treatment of patients with cancer pain are: no ceiling effect and the possibility of application in any form (oral, subcutaneous, intravenous, rectal, transmucosal, epidural, subarachnoid, and locally on skin and mucous membranes affected by disease). In cancer patients receiving morphine in analgesic doses in symptomatic treatment, respiratory depression is rare because pain is a strong agonist to the respiratory centre. In general, morphine is recommended in the oral form, and in patients with swallowing problems, the subcutaneous form should be used [9, 11, 13]. Morphine in intravenous form should be administered to people with massive peripheral oedema, coagulation disorders, and poor peripheral circulation. Morphine and oxycodone should not be used in patients with renal insufficiency due to the reduced elimination of metabolites [9, 10].

According to the recommendations of PTBB, oxycodone or oxycodone with naloxone should be the first choice in the treatment of cancer pain with a visceral component. In addition, oxycodone is an appropriate medicine for neuropathic pain [9, 10].

Fentanyl is used as a transdermal system, and in breakthrough pain it also works in sublingual, nasal, and buccal form. The biggest threat with its use is associated with drug accumulation and strong physical and mental addiction. Percutaneous forms are not suitable for the treatment of patients with unstable pain and fever [9, 18]. However, it should be remembered that in patients with breakthrough pain a first-choice analgetic should be an oral drug in an immediate release formulation, while the use of transmucosal fentanyl should be secondary. The dose of the drug in breakthrough pain should be 15–20% of the daily dose of the parent drug or another opioid after dose conversion [9, 10].

Buprenorphine is 75 times more potent than morphine; it is characterised by significant lipophilicity and is used primarily in the transdermal form. Buprenorphine as well as fentanyl and methadone can be safely used in chronic renal disease with GFR < 30 mL/min [9, 10]. Buprenorphine is the first-choice drug in the elderly and in patients with liver failure [9]. It can be used in a sublingual form in breakthrough pain.

Methadone is applicable when other strong opioids are ineffective or when their side effects occur [9, 10, 18].

Hyperalgesia is a usual side effects of all opioids. This is a paradoxical reaction with pain intensification when using opioid drugs. The mechanism is not well understood, it is thought that it may be a genetic basis for opioid receptors. In the case of hyperalgesia to a specific opioid, switching to another drug also from the opioid group is recommended. A dose reduction of opioid causing hyperalgesia and adding of coanalgesics is a scheme less recommended by PTBB [9].

Coanalgesic adjuvants

The typical analgetic drugs, which can be added on each stage of the analgesic ladder, include coanalgesics or coanalgesic adjuvants. Supportive therapy usually refers to neuropathic or bone pain. This group includes — among others — corticosteroids, anticonvulsants (carbamazepine, gabapentin), local anaesthetics, calcitonin, cannabinoids and antidepressants (e.g. tricyclic antidepressants — amitriptyline, doxepin, nortriptyline, desipramine and tetracycline antidepressants — mirtazapine, serotonin reuptake inhibitors — escitalopram, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, serotonin and epinephrine reuptake inhibitors — venlafaxine, duloxetine, milnacipran). The mechanism of action of antidepressants consists of inhibition of NMDA receptors or inhibition of noradrenaline/serotonin reuptake from the synaptic cleft, contributing to the intensification of nociception inhibition. The use of coanalgesics is helpful in treating the accompanying symptoms in oncological disease and chronic pain: insomnia, anxiety, and depression [9, 11].

Psychotherapy and other non-pharmacological methods

Psychotherapy is used in various dysfunctions and diseases, including as a complementary treatment method to pharmacotherapy in cancer patients with chronic pain. Over the last three decades Cognitive Behavioural Therapy (CBT) has been mainstreamed and has become a recommended psychotherapy method. Evidence of its effectiveness in pain problems and comprehensive pain syndromes is confirmed by numerous randomised studies. CBT is the main method dedicated to patients with pain and can be used alone or in combination with medical methods in an interdisciplinary aspect. Importantly, it is used in the treatment of all types of chronic pain, not only cancerous [19, 20].

Numerous studies show that strong pain fosters a growing sense of threat and ruminating and induces the conviction of an inability to cope with it, which is associated with the occurrence of physical and psychosocial disorders (even after controlling pain and reducing the level of depression). There are a lot of questions in the analyses regarding the occurrence of mood, anxiety, and sleep disorders in many people struggling with chronic pain, in which CBT could be applicable [19, 20].

The main goal of psychotherapy is to reduce the feeling of pain and mental suffering and to improve the physical and role functions. This is achieved by working on the change of "maladaptive" behaviours, increasing adaptive behaviour, identifying and correcting "maladaptive" thoughts and beliefs, as well as increasing self-effectiveness in coping with pain [19, 20].

There is no standard algorithm or procedure for analgesic treatment using psychotherapy in the CBT paradigm. The time devoted to the clinical diagnosis, evaluation, and number of sessions and therapeutic techniques used is individual and diverse. The most commonly used techniques include relaxation training, setting and working towards behavioural goals (usually involving systematic increase in physical activity and other activities), behavioural activation, activity stimulation tips, problem-solving education, and cognitive restructuring. Typically, in cognitive-behavioural therapy, there are exercises between therapeutic sessions to train and apply new skills (e.g. thought recording, relaxation practice, work on behavioural goals) [17, 19, 20].

The effectiveness of CBT in the treatment of chronic pain has been confirmed by meta-analyses and numerous opinions, which, however, emphasise the role of CBT as part of the therapeutic program alongside pharmacotherapy and the patient's own work [19, 20].

Among other methods supporting the process of pain treatment, one should mention hypnosis, which acts by lowering distress (demotivating — harmful stress), and relaxation and meditation methods. An important method is psychoeducation, which is designed to educate patients of understanding and ways of communicating the problems related to pain, anxiety, and depressed mood. The effect of psychoeducation is to increase the sense of self-efficacy and certainty as to the ability to deal with it. Research results indicate that education, hypnosis, relaxation, and visualisation support the acquisition of stress management skills and, independently of analgesics, may reduce the intensity of pain. These effects are so significant that they should be considered

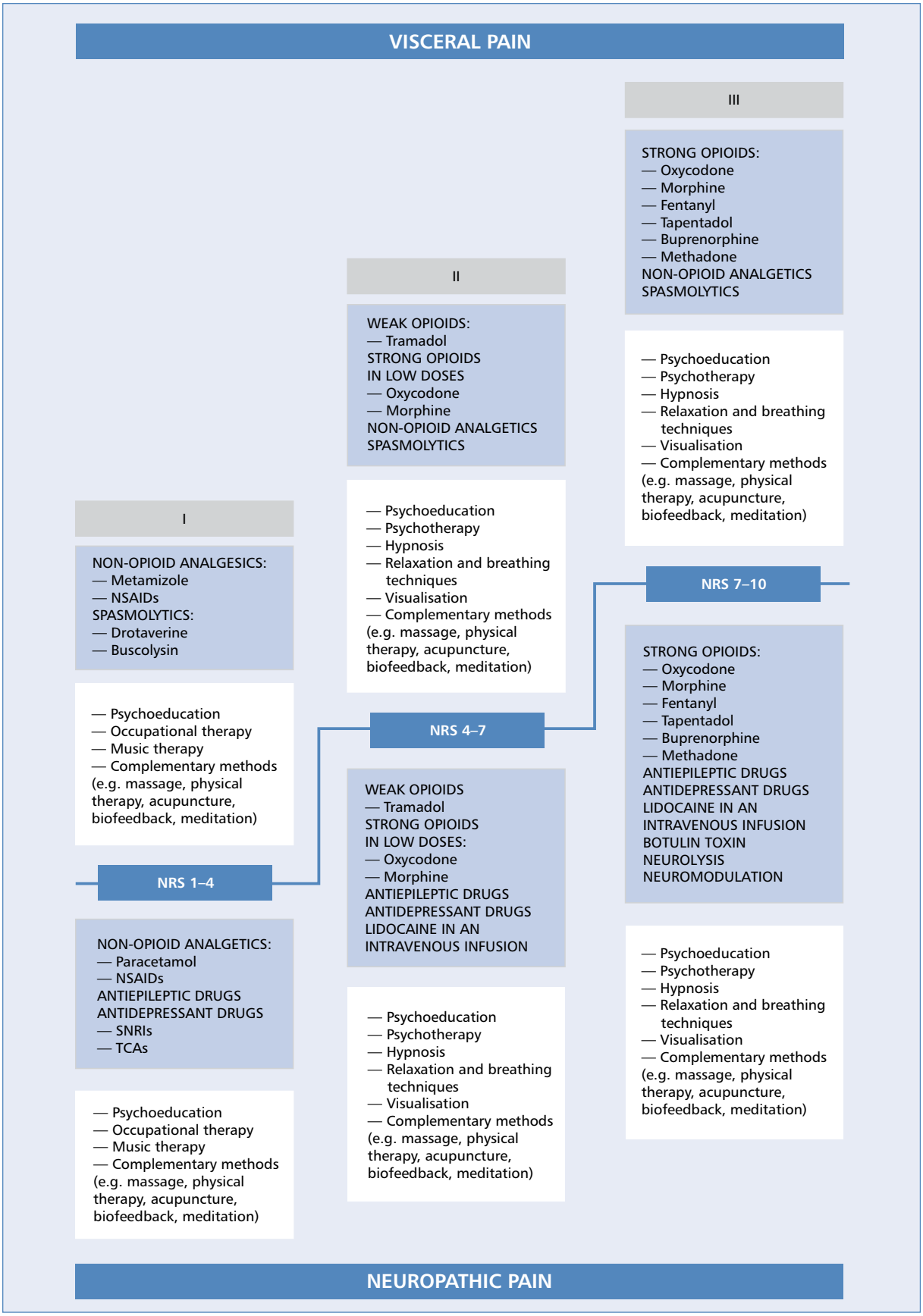

Figure 1. Interdisciplinary treatment of chronic pain. Own elaboration based on literature included in the bibliography

as the standard elements of care for patients treated for cancer pain [17, 20, 21].

It is undeniable that psychological factors contribute to an increase in the pain and suffering experienced by the patient. However, knowledge about the aetiology of pain and methods of optimal coping with it are insufficient, and questions about which strategies are the most effective for which pain syndromes remain unanswered. There is a need for professional integration of people with specialist knowledge in the field of pain treatment, at both the medical and psychological levels [19–21].

Issues regarding the treatment of pain and care of patients at the request of the Polish Society for the Study of Pain were legally enshrined in the amendment to the Law on Patients' Rights and the Patient's Rights Ombudsman of May 11, 2017. In Chapter 6, art. 20, p. 13 we can read:

"1. *The patient has the right to pain treatment.*
2. *The entity providing health services is obliged to take actions to determine the degree of pain intensity, treat pain, and monitor the effectiveness of this treatment*".

According to the aforementioned, it is the duty of the medical personnel not only to apply the treatment in connection with the underlying disease, but also to conduct the treatment in connection with the accompanying painful ailments. Therefore, the patient has the right to require appropriate analgesics from every doctor and health care facility [22].

Summary

Pain is a phenomenon and experience not only physical but also emotional, psychosocial, and spiritual. In connection with the perception of psychological and existential needs related to pain, the necessity to supplement therapeutic procedures has arisen. According to this idea, the treatment of chronic pain in the course of cancer cannot be limited to pharmacological treatment alone, and psychotherapeutic methods should not be treated as an addition or as an alternative to pharmacological treatment of pain. Figure 1 presents a proposal for the treatment of chronic pain, in which, on the basis of the analgetic ladder, pharmacological and non-pharmacological methods of pain therapy according to its intensity and aetiology are presented (divided into visceral and neuropathic pains). Supportive methods were considered such as physiotherapy, visualisation techniques, relaxation techniques, crisis interventions, methods using art and music, desensitisation, and others. Coanalgesics or additional agents (e.g. bisphosphonates, denosumab, or glucocorticosteroids and non-pharmacological treatment techniques — localised radiotherapy, radioisotopes in multifocal pain, percutaneous TENS nerve electrical stimulation, epidural or spinal analgesia, and others) should be a complement.

One should always take an individual approach to therapeutic interactions based on the patient's needs and personal features. It is necessary to take into account the purpose of such therapy, consisting of increasing the sense of pain control and significantly improving patients' quality of life. These procedures should also focus on psychosocial support and provide appropriate education for the families and relatives of the patient. The above activities increase the patient's sense of control and reduce the level of helplessness of caregivers and family. Pharmacological treatment is commonly insufficient and can be associated with a multitude of side effects or a lack of therapeutic effects. Integrated treatment of people with chronic pain will significantly reduce its level or completely eliminate it, which in turn will translate into restoring the patient's will to continue their lives and give them strength to deal with the disease. Achieving success on this basis is associated with the necessity of close cooperation between oncologist and a psychooncologist or psychologist, preferably at the level of a multidisciplinary team (MDT).

References

1. Rucińska M. Choroba nowotworowa — wprowadzenie. Choroba nowotworowa a inne choroby przewlekłe — etiologia, epidemiologia, rokowanie. In: Praktyczny podręcznik psychoonkologii dorosłych. Rogiewicz M (ed.). Medycyna Praktyczna, Kraków 2015: 23.
2. Machowska R. Marciniak B. Terapia poznawczo-behawioralna bólu w przebiegu choroby nowotworowej — podejście spersonalizowane. Psychoonkologia. 2016; 20(3): 142–153.
3. De Walden-Gałuszko K. Jakie są psychologiczne reakcje na niektóre objawy somatyczne? Ból. In: Psychoonkologia w praktyce klinicznej. Wydawnictwo Lekarskie PZWL, Warszawa 2015: 29–33.
4. Kupla M. Stypuła-Ciuba B. Ból nowotworowy i uciążliwość objawów somatycznych a jakość życia u pacjentów z chorobami nowotworowymi. Medycyna Paliatywna. 2013; 5(4): 171–179.
5. Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. J Pain Res. 2016; 9: 515–534, doi: 10.2147/JPR.S97759, indexed in Pubmed: 27524918.
6. Rolf-Detlef T, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain. 2015; 156(6): 1003–1008, doi: 10.1097/j.pain.0000000000000160.
7. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, et al. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage. 2016; 51(6): 1070–1090.e9, doi: 10.1016/j.jpainsymman.2015.12.340, indexed in Pubmed: 27112310.
8. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. J Clin Oncol. 2014; 32: 4149e4154.
9. Wordliczek J, Kotlińska-Lemieszek A, Leppert W, et al. Farmakoterapia bólu u chorych na nowotwory — zalecenia Polskiego Towarzystwa Badania Bólu, Polskiego Towarzystwa Medycyny Paliatywnej, Polskiego Towarzystwa Onkologicznego, Polskiego Towarzystwa Medycyny Rodzinnej, Polskiego Towarzystwa Anestezjologii i Intensywnej Terapii. PTBB. Ból. 2017; 18(3): 11–53.
10. Fallon M, Giusti R, Aielli F, et al. ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018; 29(Supplement_4): iv166–iv191, doi: 10.1093/annonc/mdy152, indexed in Pubmed: 30052758.
11. Krajnik M, Leppert W. Ból w chorobie nowotworowej. In: Kompendium leczenia bólu. Milewska-Malec M, Woroń J (ed.). Wydawnictwo Termedia, Warszawa 2017: 563–576.

12. Wordliczek J. Rodzaje bólu i mechanizmy ich powstawania. In: Kompendium leczenia bólu. Milewska-Malec M, Woroń J (ed.). Wydawnictwo Termedia, Warszawa 2017: 13–19.
13. Ciałkowska-Rysz A. Farmakoterapia bólu nowotworowego Clin Exp MED Lett. 2006; 47(1): 3–8.
14. Stanowisko Polskiego Towarzystwa Badania Bólu dot. skal oceny nasilenia bólu. Dostępne online: https://ptbb.pl/zasoby/pobierz-pliki/category/42-stanowisko-ptbb-dot-skal-oceny-nasilenia-bolu. 11-12-2018.
15. Bisaga W, Dorazil M, Dobrogowski J, et al. Porównanie przydatności wybranych skal oceny bólu neuropatycznego u pacjentów z przewlekłymi zespołami bólowymi: krótkie doniesienie. Medycyna Paliatywna w Praktyce. 2011; 5(1): 22–26.
16. Jarosz J. (ed.) Postępowanie w bólach nowotworowych. Zalecenie postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych — 2013. Polskie Towarzystwo Onkologii Klinicznej. Dostępne online: http://onkologia.zalecenia.med.pl/.
17. Krzakowski M. (konsultacja merytoryczna), Zagozda M, Cieślak K, Gołąb D, (konsultacja psychoonkologiczna). Ból w chorobie nowotworowej. Tłumaczenie z National Cancer Institute of United States„Support for People With Cancer. When Cancer Returns PRIMOPRO. 2018; 9.
18. Ciałkowska-Rysz A, Dzierżanowski T. Podstawowe zasady farmakoterapii bólu u chorych na nowotwory i inne przewlekłe, postępujące, zagrażające życiu choroby. Medycyna Paliatywna. 2014; 6(1): 1–6.
19. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol. 2014; 69(2): 153–166, doi: 10.1037/a0035747, indexed in Pubmed: 24547801.
20. Syrjala KL, Jensen MP, Mendoza ME, et al. Psychological and behavioral approaches to cancer pain management. J Clin Oncol. 2014; 32(16): 1703–1711, doi: 10.1200/JCO.2013.54.4825, indexed in Pubmed: 24799497.
21. Paice JA, Ferrell B. The management of cancer pain. CA Cancer J Clin. 2011; 61(3): 157–182, doi: 10.3322/caac.20112, indexed in Pubmed: 21543825.
22. Ustawa z dnia 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta; nowelizacja ustawy o prawach pacjenta i Rzeczniku Praw Pacjenta z dnia 11 maja 2017.

VIA MEDICA

CASE REPORT

Kamila Patrycja Kidrycka[1], Justyna Burzyńska-Śliwowska[1], Rafał Maksim[2], Andrzej Namiot[4], Marek Z. Wojtukiewicz[4], Ewa Sierko[2, 4]

[1]Institute of Diagnostic Imaging of the Oncology Centre in Białystok, Poland
[2]Radiotherapy Institute of the Oncology Centre in Białystok, Poland
[3]Institute of Anatomy, Białystok Medical University, Poland
[4]Department of Oncology, Białystok Medical University, Poland

Angiosarcoma — a malignant neoplasm secondary to radiotherapy for breast cancer in a female patient following breast-conserving treatment — a case report

Address for correspondence:
Dr hab. n. med. Ewa Sierko
Klinika Onkologii,
Uniwersytet Medyczny w Białymstoku
e-mail: ewa.sierko@iq.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 217–222
DOI: 10.5603/OCP.2019.0012
Translation: dr Elżbieta Stelmaszczyk

ISSN 2450–1654

ABSTRACT

Angiosarcoma is a rare malignant neoplasm, accounting for 1–2% of all sarcomas. The main cause of developing secondary angiosarcoma is radiotherapy. We analysed the case of a 52-year-old woman with breast cancer, who had undergone breast-conserving therapy. Four years after finishing treatment, she was diagnosed with secondary angiosarcoma in the irradiated area. The patient underwent a mastectomy. The disease relapsed six months after the operation in form of local recurrence, as well as liver and lung metastases. The patient's condition gradually deteriorated despite treatment (chemotherapy and symptomatic management). The patient died due to cardiorespiratory failure nine months after the diagnosis of secondary malignancy.

Key words: angiosarcoma, breast cancer, chemotherapy, secondary malignant neoplasm, radiotherapy

Oncol Clin Pract 2019; 15, 4: 217–222

Introduction

The incidence of sarcomas in Poland is estimated at 2/100,000 per year; 1–2% of them are angiosarcomas (AS) [1, 2], which are soft tissue sarcomas stemming from the endothelial cells of blood or lymphatic vessels [3]. The most common locations of this tumour are the head, breast, and the limbs [4]. These neoplasms may occur as primary tumours, with no influence of external factors, or as secondary tumours — usually following radiotherapy (RT). The latter constitute about 0.5–5% of all sarcomas [5, 6]. Although the secondary AS of the breast is very rare and constitutes about 0.9 per 1000 cases of malignant neoplasms of the breast, they are an important clinical issue because they are characterised by a poor prognosis. It is estimated that their number will grow due to the higher incidence of breast cancer and the use of RT in breast-conserving treatment [7–9].

Below, we present the case of a 52-year-old female breast cancer patient who had previously undergone breast-conserving therapy with a radical goal. Four years after finishing the above treatment, an AS with a high grade of malignancy was diagnosed in the RT area.

Case report

A 47-year-old woman came in for mammography (MMG) in November 2012, which showed a lesion of increased density with malignant characteristics (BI-RADS 5), about 19 mm in size, in the upper exterior quadrant of the left breast, within 2 cm of the areola.

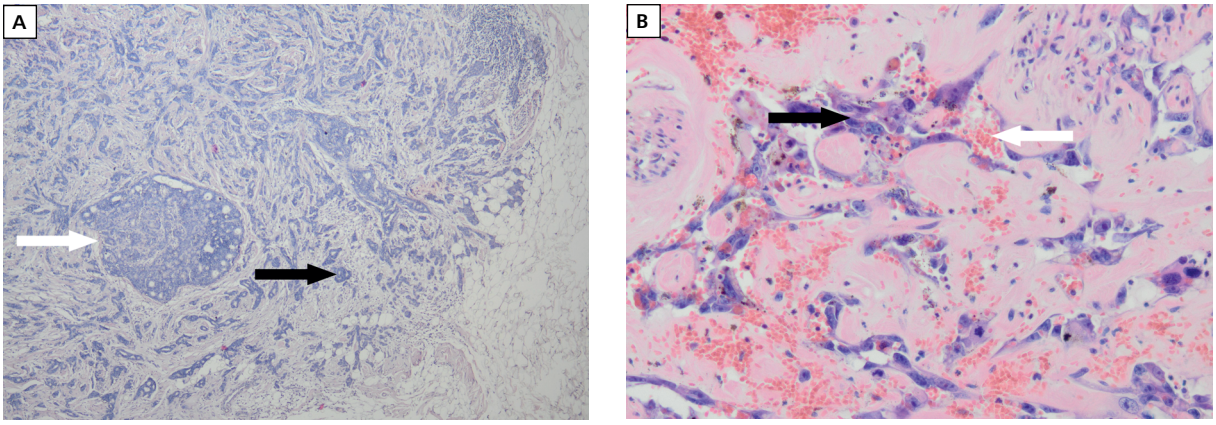

Figure 1. Pathology images of right breast tumour **A.** G2 Duct carcinoma (black arrow) and a lesion of non-invasive duct carcinoma (white arrow) (4× magnification). **B.** Angiosarcoma with a high malignancy level — pathological vascular fissures (white arrow) lined with abnormal neoplastic cells (black arrow) (20× magnification)

In an ultrasonographically (USG) controlled fine-needle biopsy of the above-mentioned lesion, the presence of malignant cells was confirmed. In the same month, the patient underwent breast-conserving surgery (excision of the upper external quadrant along with the sentinel lymph node). In a surgical pathology test, metastases to the sentinel lymph node were detected, and a decision was made to excise the remaining axillary lymph nodes. The lesion was excised completely — macroscopically as well as microscopically. In a post-operative pathology examination, the presence of invasive grade 2 (G2) ductal carcinoma (Figure 1A) was detected, with estrogen receptor (ER) expression in 80% of the tumour cells, and progesterone receptor (PR) expression in 90% of the cells, but no human epidermal growth factor receptor 2 (HER2) expression was found and Ki-67 cell proliferation marker was present in 5% of the tumour cells. Distally, focal lesions of ductal carcinoma *in situ* (DCIS) were present. Metastases to one of the eight excised lymph nodes were detected. The clinical stage of the disease was marked as pT2N1M0.

The patient received four cycles of adjuvant chemotherapy (AC regimen — doxorubicin and cyclophosphamide) from January 2013 until March 2013, with subsequent adjuvant hormonal therapy with tamoxifen at a daily dose of 20 mg (beginning in March 2013). From April 2013 until June 2013, the patient was treated with postoperative radiotherapy for the area of the right breast, in radiation conditions of × 4MV, × 6MV up to a total dose of 50 Gy/2 Gy/in 25 fractions. For the post-operative area, the total dose was raised to 66 Gy/2 Gy/in 33 fractions. During radiotherapy, an acute cutaneous post-radiation reaction occurred with a G2 intensity in the RTOG scale, which healed after a month's time.

In August of 2013, after the acute reaction had healed, redness and swelling of the skin of the right breast appeared again, and remained throughout the time during which routine examinations were conducted. On imaging — MMG and USG — performed outside of our hospital, no evidence of recurrent disease was detected. In July 2017, four years after completing radiotherapy, a cyanotic lesion on the skin of the right breast appeared, along with a small ulceration in the proximity of the nipple. Antibiotics and anti-coagulants were prescribed. Due to the continuing presence of the above-mentioned lesions, in December of 2017 samples were taken from the ulcerated lesion near the nipple (Figure 2A). Pathology examination revealed AS — a malignant neoplasm secondary to radiotherapy (Figure 1B). Computed tomography (CT) scans showed no evidence of distal metastases. The patient underwent mastectomy in January 2018. In July 2018, on imaging done outside of our hospital, metastases to the lungs and liver were shown. On examination upon hospital admission, traits of local recurrence were observed in the form of lumps in the scar from the right-side mastectomy. In August 2018, half a year after the surgery, the patient underwent palliative chemotherapy (ADIC regimen — doxorubicin and dacarbazine). After the first cycle of this treatment, laboratory testing showed anaemia and G3 neutropaenia. Treatment with granulocyte growth factor was applied, along with symptomatic treatment, and the patient's condition improved. Within the same month, due to increasing dyspnea and recurring fluid in the pleural cavity (after draining the right pleural cavity twice), and clinical recurrence, a control CT scan was performed. The test showed local recurrence, metastases to the lungs and liver, a significant amount of fluid in the pleural cavity, and fungal lesions in the lungs (Figure 2B, C, D). In order to lessen the symptoms, talc pleurodesis was performed. In September 2018, in an angio-CT scan of the thorax, a sub-segmental pulmonary embolism was detected, along with progression of local infiltration and

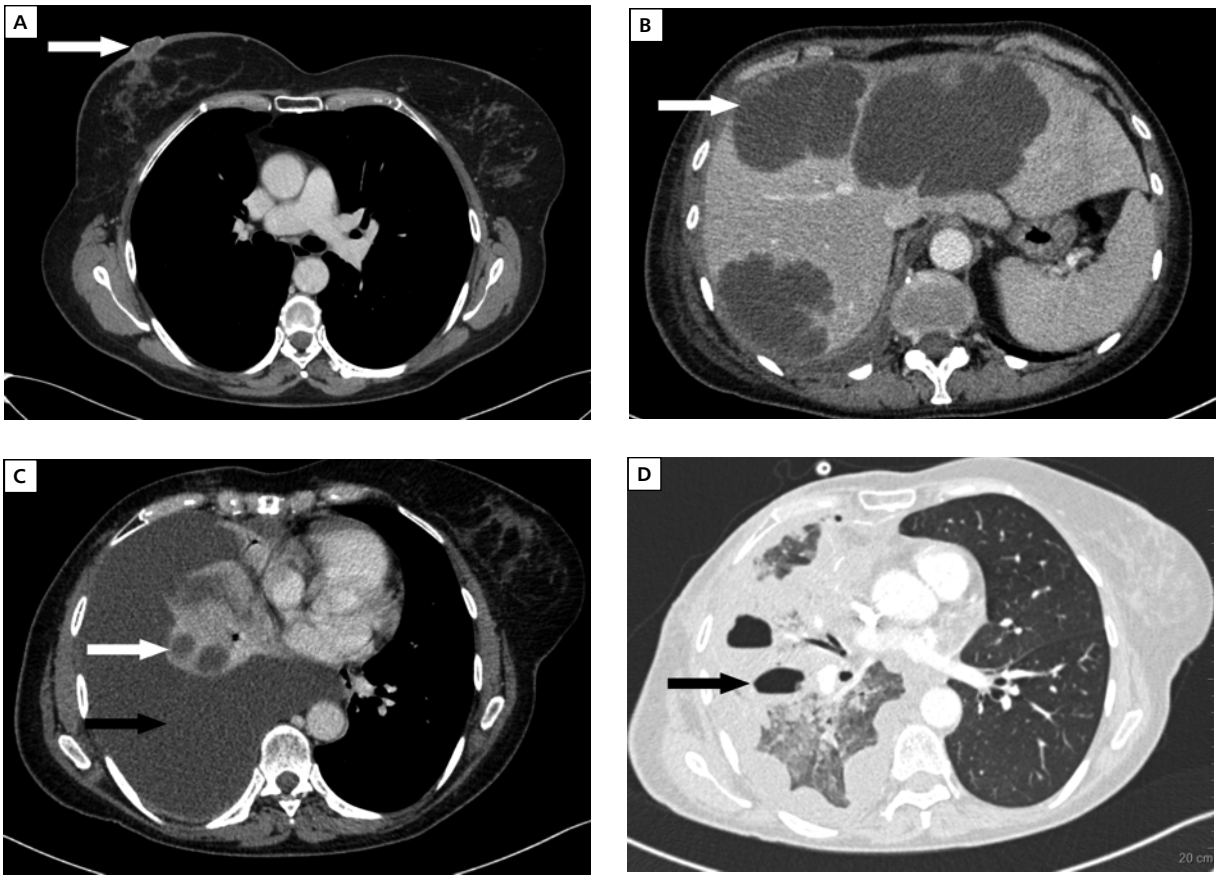

Figure 2. Angiosarcoma in a 53-year-old female patient, 4 years after completion of radical treatment of breast cancer (breast-conserving surgery, radiotherapy, chemotherapy). Computed tomography following contrast administration (venous phase). **A.** Tumour of right nipple-surrounding area (white arrow). Testing conducted previous to treatment (January 2018). **B.** Cystic metastases of angiosarcoma to the liver (white arrow), Testing conducted after chemotherapy (August 2018). **C.** Cystic metastases to the lungs (white arrow) and free flood in the pleural cavity (black arrow). Test conducted after chemotherapy (August 2018). **D.** Fungal cavities in the right lung (black arrow) — lung window. Testing conducted after chemotherapy (September 2018)

enlargement of fungal lesions in the lungs. The patient was given anti-fungal treatment and the best possible symptomatic treatment. Despite treatment, the patient's state gradually worsened, and in September 2018 she died due to cardiorespiratory insufficiency.

Discussion

Angiosarcomas are very rare tumours, characterised by a high level of malignancy [10]. Factors predisposing towards the development of AS are: previous radiotherapy, exposure to polyvinyl chloride, arsenic, and thorium dioxide, chronic swelling (described as Steward-Trewes syndrome in related literature), and probably exposure to UV radiation (especially cutaneous sarcomas of the head) [4, 10–16]. No co-occurrence with genetic syndromes has been proven, although 3% of patients with AS are diagnosed with Ollier's disease, Maffuci disease, von Recklinghausen syndrome, retinoblastoma, or xeroderma pigmentosum [4, 13, 17–19].

In a retrospective study, Kirova YM et al. [20] showed that of 13,472 patients who underwent radiotherapy due to early breast cancer, 35 developed sarcomas (48% — 12 patients had breast AS and 1 patient was found to have AS of thoracic region). The cumulated risk of RT-induced sarcoma has been calculated to be 0.27% after 10 years, and 0.48% 15 years after treatment with radiation. The standardised incidence ratio (SIR) for sarcomas in patients with breast cancer, who previously underwent radiation therapy, has been calculated at 10.2; however, in women who did not receive RT, the SIR amounts to 1.3. Yap et al. [7] also observed an increase in sarcoma incidence in the area submitted to radiation. Among them, AS amounted to 56.8% of cases. However, in those who did not undergo RT, only

5.7% developed this malignancy. In a study by Huang et al. [21], an increased incidence of soft-tissue sarcomas was also confirmed (especially AS), in patients who had undergone RT due to breast cancer. The standardised incidence factor in the case of AS secondary to RT has been estimated at 26.2, and 2.1 in women who were not treated with RT.

It is thought that the highest incidence of radiation-induced AS is in patients undergoing treatment for breast cancer of lymphoma [7, 21, 22]. The latency period from completion of RT to the development of breast AS varies from 3 to 25 years [15, 23–26]. The pathological mechanism of RT's influence on the development of AS is not fully known yet. It suggests that radiation dosages above 50 Gy cause cellular apoptosis, and doses below 50 Gy cause DNA damage and instability. Sarcomas often occur on the area surrounding the irradiated body part, where doses may vary [23, 24]. Attempts at modifying the radiation dosage, volume of the body space being irradiated, and the total RT time in breast cancer patients are being made in order to lower the risk of recurrent disease, as well as the occurrence of late-onset radiation complications [27–29].

A primary breast AS usually occurs in women aged 30–50 years as a lump of the breast, whereas the secondary AS usually develops in women aged over 60 years as a cutaneous lesion (a blue-cherry colour lump, swelling, erythematous patches) [15, 16, 26].

On imaging (USG, MMG), sarcomas of the breast give nonspecific symptoms — usually a thickening and swelling of the skin, similar to the lesions present in most women who undergo breast-conserving therapy and supplementary radiotherapy. This causes a delay in diagnosis and treatment. In the case of suspicion of a breast AS, the best imaging test is MRI [9, 30, 31]. The final diagnosis of AS is made based on the results of pathological testing [32, 33].

The tumours being discussed — besides a high rate of local recurrences — are characterised by a relatively high rate of distal metastases and are associated with poor prognosis. The most important prognostic factors related to poor outcomes are: the diameter of the tumour, the depth of infiltration, positive surgical margins, the presence of metastases, or local recurrence after surgical resection [23, 34, 35]. The most common sites of distal metastases are the lungs [16, 36], but liver, cecum, tonsillar, cheek, oral cavity, and heart metastases are also documented. [37–40].

The only chance of cure in patients with secondary AS is when R0 margins are achieved during surgery [41, 42]. In a case series of 14 patients observed for 12 years, a non-radical resection of the tumour was associated with rapid local recurrence and poor prognosis. The average survival time of patients who had undergone extensive surgery amounted to 42 months, when compared to six months in people who did not achieve R0 margins [24]. However, in a study by Seinen et al. [23], in 14 out of 24 patients who underwent a mastectomy, a surgical margin free of malignancy was achieved, when compared to two out of seven patients who underwent a tumour resection with a macroscopic margin equal to or greater than 2 cm. Only 3 women underwent an extensive resection of the area subjected to radiation, and in 2 of these patients the surgical margin was free of tumour cells. Despite achieving R0 margins in these patients, in about 2/3 of these patients local recurrence took place, and the median survival specific to the disease was 37 months.

In the case of AS, RT may be considered, although most radiation oncologists are not very willing to apply it to an area which was previously irradiated. Some authors claim that hyper-fractioned adjuvant RT after surgery may be a promising method of secondary AS treatment. [43–45].

So far, there has been a lack of unequivocal data regarding adjuvant chemotherapy in this indication [4, 17, 46, 47]. The most effective agents are doxorubicin and ifosfamide [48]. Some studies have proven that simultaneous treatment with neoadjuvant chemotherapy and hyperthermia in patients with poor prognostic soft tissue sarcoma results in better survival [49].

Currently, the greatest hope in treating sarcoma patients is based on the molecular biology evolution. Bevacizumab, sorafenib, and pazopanib were studied among other agents [50, 51]. A varied response to treatment with sorafenib and bevacizumab was found [51–53]. In the case of pazopanib, an improvement in progression-free survival was found; however, the effectiveness of the drug may be limited due to the sarcoma's acquisition of immunity to a given therapy [54, 55]. Anti-angiogenic treatment may play a role in some soft tissue therapy, which is why further research is necessary for the planning of effective therapeutic regimens [51, 52].

In conclusion, malignant neoplasm secondary to RT — an AS with a high level of malignancy — developed just four years after irradiation. The disease course was aggresive — just a month after surgical resection due to AS, local recurrence appeared, along with metastases to the lungs and liver. The patient survived only nine months after receiving the diagnosis. Studies aimed at identifying factors that amplify the risk of acquiring AS secondarily to RT are needed. Awareness regarding late-onset complications of RT, such as secondary neoplasms, should be raised among doctors who are responsible for patient observation, in order for the earliest possible detection to take place.

References

1. Ducimetière F, Lurkin A, Ranchère-Vince D, et al. Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. PLoS One. 2011; 6(8): e20294, doi: 10.1371/journal.pone.0020294, indexed in Pubmed: 21826194.
2. Jodkiewicz Z, Kozakiewicz B, Roszkowska-Purska K, et al. Angiosarcoma w obszarze napromienianym po 16 latach obserwacji u chorej na raka piersi leczonej oszczędzająco — analiza przypadku. Nowotwory Journal of Oncology. 2014; 64(5): 396–400.
3. Buehler D, Rice SR, Moody JS, et al. Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. Am J Clin Oncol. 2014; 37(5): 473–479, doi: 10.1097/COC.0b013e31827e4e7b, indexed in Pubmed: 23428947.
4. Young RJ, Woll PJ, Staton CA, et al. Angiosarcoma. Lancet Oncol. 2010; 11(10): 983–991, doi: 10.1016/S1470-2045(10)70023-1, indexed in Pubmed: 20537949.
5. Arora TK, Terracina KP, Soong J, et al. Primary and secondary angiosarcoma of the breast. Gland Surg. 2014; 3(1): 28–34, doi: 10.3978/j.issn.2227-684X.2013.12.03, indexed in Pubmed: 25083491.
6. Sheppard DG, Libshitz HI. Post-radiation sarcomas: a review of the clinical and imaging features in 63 cases. Clin Radiol. 2001; 56(1): 22–29, doi: 10.1053/crad.2000.0599, indexed in Pubmed: 11162693.
7. Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys. 2002; 52(5): 1231–1237, indexed in Pubmed: 11955733.
8. Thijssens KMJ, van Ginkel RJ, Suurmeijer AJH, et al. Radiation-induced sarcoma: a challenge for the surgeon. Ann Surg Oncol. 2005; 12(3): 237–245, doi: 10.1245/ASO.2005.03.041, indexed in Pubmed: 15827816.
9. Mery CM, George S, Bertagnolli MM, et al. Secondary sarcomas after radiotherapy for breast cancer: sustained risk and poor survival. Cancer. 2009; 115(18): 4055–4063, doi: 10.1002/cncr.24462, indexed in Pubmed: 19526590.
10. Buehler D, Rice SR, Moody JS, et al. Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. Am J Clin Oncol. 2014; 37(5): 473–479, doi: 10.1097/COC.0b013e31827e4e7b, indexed in Pubmed: 23428947.
11. Fodor J, Orosz Z, Szabó E, et al. Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature. J Am Acad Dermatol. 2006; 54(3): 499–504, doi: 10.1016/j.jaad.2005.10.017, indexed in Pubmed: 16488303.
12. Billings SD, McKenney JK, Folpe AL, et al. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. Am J Surg Pathol. 2004; 28(6): 781–788, indexed in Pubmed: 15166670.
13. Penel N, Grosjean J, Robin YM, et al. Frequency of certain established risk factors in soft tissue sarcomas in adults: a prospective descriptive study of 658 cases. Sarcoma. 2008; 2008: 459386, doi: 10.1155/2008/459386, indexed in Pubmed: 18497869.
14. Berebichez-Fridman R, Deutsch YE, Joyal TM, et al. Stewart-Treves Syndrome: A Case Report and Review of the Literature. Case Rep Oncol. 2016; 9(1): 205–211, doi: 10.1159/000445427, indexed in Pubmed: 27099606.
15. Hui A, Henderson M, Speakman D, et al. Angiosarcoma of the breast: a difficult surgical challenge. Breast. 2012; 21(4): 584–589, doi: 10.1016/j.breast.2012.01.001, indexed in Pubmed: 22305554.
16. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. Ann Surg Oncol. 2013; 20(4): 1267–1274, doi: 10.1245/s10434-012-2755-y, indexed in Pubmed: 23224828.
17. Penel N, Marréaud S, Robin YM, et al. Angiosarcoma: state of the art and perspectives. Crit Rev Oncol Hematol. 2011; 80(2): 257–263, doi: 10.1016/j.critrevonc.2010.10.007, indexed in Pubmed: 21055965.
18. Forman D, Bennett B, Stafford J, et al. Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases. Br J Ind Med. 1985; 42(11): 750–753, indexed in Pubmed: 4063218.
19. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 2005; 11(3): 241–247, indexed in Pubmed: 16053668.
20. Kirova YM, Gambotti L, De Rycke Y, et al. Radiation-induced sarcomas after radiotherapy for breast carcinoma: a large-scale single-institution review. Cancer. 2005; 104(4): 856–863, doi: 10.1002/cncr.21223, indexed in Pubmed: 15981282.
21. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer. 2001; 92(1): 172–180, indexed in Pubmed: 11443624.
22. Virtanen A, Pukkala E, Auvinen A. Angiosarcoma after radiotherapy: a cohort study of 332,163 Finnish cancer patients. Br J Cancer. 2007; 97(1): 115–117, doi: 10.1038/sj.bjc.6603805, indexed in Pubmed: 17519906.
23. Seinen JM, Styring E, Verstappen V, et al. Radiation-associated angiosarcoma after breast cancer: high recurrence rate and poor survival despite surgical treatment with R0 resection. Ann Surg Oncol. 2012; 19(8): 2700–2706, doi: 10.1245/s10434-012-2310-x, indexed in Pubmed: 22466664.
24. Jallali N, James S, Searle A, et al. Surgical management of radiation--induced angiosarcoma after breast conservation therapy. Am J Surg. 2012; 203(2): 156–161, doi: 10.1016/j.amjsurg.2010.12.011, indexed in Pubmed: 21658671.
25. Li GZ, Fairweather M, Wang J, et al. Cutaneous radiation-associated breast angiosarcoma: radicality of surgery impacts survival. Ann Surg. 2017; 265(4): 814–820, doi: 10.1097/SLA.0000000000001753, indexed in Pubmed: 28267696.
26. Morgan EA, Kozono DE, Wang Q, et al. Cutaneous radiation-associated angiosarcoma of the breast: poor prognosis in a rare secondary malignancy. Ann Surg Oncol. 2012; 19(12): 3801–3808, doi: 10.1245/s10434-012-2563-4, indexed in Pubmed: 22890593.
27. Bentzen SM, Agrawal RK, Aird EGA, et al. START Trialists' Group, START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008; 371(9618): 1098–1107, doi: 10.1016/S0140-6736(08)60348-7, indexed in Pubmed: 18355913.
28. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control andn survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 2881-10882 trial. J Clin Oncol. 2007; 25: 3259–3265, doi: 10.1200/JCO.2007.11.499.1.
29. Vicini FA, Winter K, Wong J, et al. Initial efficacy results of RTOG 0319: Three dimensional conformal radiation therapy (3D-CRT) confined to the region of the lumpectomy cavity for stage I/II breast carcinoma. Int J Radiat Oncol Biol Phys. 2008; 72(1): S3, doi: 10.1016/j.ijrobp.2009.06.067.
30. Yang WT, Hennessy BTJ, Dryden MJ, et al. Mammary angiosarcomas: imaging findings in 24 patients. Radiology. 2007; 242(3): 725–734, doi: 10.1148/radiol.2423060163, indexed in Pubmed: 17325063.
31. O'Neill AC, D'Arcy C, McDermott E, et al. Magnetic resonance imaging appearances in primary and secondary angiosarcoma of the breast. J Med Imaging Radiat Oncol. 2014; 58(2): 208–212, doi: 10.1111/1754-9485.12100, indexed in Pubmed: 24112469.
32. Hart J, Mandavilli S. Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis. Arch Pathol Lab Med. 2011; 135(2): 268–272, doi: 10.1043/1543-2165-135.2.268, indexed in Pubmed: 21284449.
33. Li N, Cusidó MT, Navarro B, et al. Breast sarcoma. A case report and review of literature. Int J Surg Case Rep. 2016; 24: 203–205, doi: 10.1016/j.ijscr.2016.04.033, indexed in Pubmed: 27281361.
34. Morgan MB, Swann M, Somach S, et al. Cutaneous angiosarcoma: a case series with prognostic correlation. J Am Acad Dermatol. 2004; 50(6): 867–874, doi: 10.1016/j.jaad.2003.10.671, indexed in Pubmed: 15153886.
35. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. Cancer. 1981; 48(8): 1907–1921, indexed in Pubmed: 7197190.
36. Nicolas MM, Nayar R, Yeldandi A, et al. Pulmonary metastasis of a postradiation breast epithelioid angiosarcoma mimicking adenocarcinoma. A case report. Acta Cytol. 2006; 50(6): 672–676, doi: 10.1159/000326039, indexed in Pubmed: 17152281.
37. Tateishi U, Yamaguchi U, Seki K, et al. Bone and soft-tissue sarcoma: preoperative staging with fluorine 18 fluorodeoxyglucose PET/CT and conventional imaging. Radiology. 2007; 245(3): 839–847, doi: 10.1148/radiol.2453061538, indexed in Pubmed: 18024454.
38. Allison KH, Yoder BJ, Bronner MP, et al. Angiosarcoma involving the gastrointestinal tract: a series of primary and metastatic cases. Am J Surg Pathol. 2004; 28(3): 298–307, indexed in Pubmed: 15104292.
39. Bar R, Netzer A, Ostrovsky D, et al. Abrupt tonsillar hemorrhage from a metastatic hemangiosarcoma of the breast: case report and literature review. Ear Nose Throat J. 2011; 90(3): 116–120, indexed in Pubmed: 21412741.
40. Baum JK, Levine AJ, Ingold JA. Angiosarcoma of the breast with report of unusual site of first metastasis. J Surg Oncol. 1990; 43(2): 125–130, indexed in Pubmed: 2406508.

41. Lindford A, Böhling T, Vaalavirta L, et al. Surgical management of radiation-associated cutaneous breast angiosarcoma. J Plast Reconstr Aesthet Surg. 2011; 64(8): 1036–1042, doi: 10.1016/j.bjps.2011.02.014, indexed in Pubmed: 21377947.
42. Al-Benna S, Poggemann K, Steinau HU, et al. Diagnosis and management of primary breast sarcoma. Breast Cancer Res Treat. 2010; 122(3): 619–626, doi: 10.1007/s10549-010-0915-y, indexed in Pubmed: 20480227.
43. Feigenberg SJ, Mendenhall NP, Reith JD, et al. Angiosarcoma after breast-conserving therapy: experience with hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys. 2002; 52(3): 620–626, indexed in Pubmed: 11849782.
44. Palta M, Morris CG, Grobmyer SR, et al. Angiosarcoma after breast-conserving therapy: long-term outcomes with hyperfractionated radiotherapy. Cancer. 2010; 116(8): 1872–1878, doi: 10.1002/cncr.24995, indexed in Pubmed: 20162708.
45. Mark RJ, Poen JC, Tran LM, et al. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer. 1996; 77(11): 2400–2406, doi: 10.1002/(SICI)1097-0142(19960601)77:11<2400::AID-CNCR32>3.0.CO;2-Z, indexed in Pubmed: 8635113.
46. Fayette J, Martin E, Piperno-Neumann S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol. 2007; 18(12): 2030–2036, doi: 10.1093/annonc/mdm381, indexed in Pubmed: 17974557.
47. Abraham JA, Hornicek FJ, Kaufman AM, et al. Treatment and outcome of 82 patients with angiosarcoma. Ann Surg Oncol. 2007; 14(6): 1953–1967, doi: 10.1245/s10434-006-9335-y, indexed in Pubmed: 17356953.
48. Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. Am J Clin Oncol. 1998; 21(3): 317–321, indexed in Pubmed: 9626808.
49. Issels RD, Lindner LH, Verweij J, et al. European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial. JAMA Oncol. 2018; 4(4): 483–492, doi: 10.1001/jamaoncol.2017.4996, indexed in Pubmed: 29450452.
50. Forscher C, Mita M, Figlin R. Targeted therapy for sarcomas. Biologics. 2014; 8: 91–105, doi: 10.2147/BTT.S26555, indexed in Pubmed: 24669185.
51. Young RJ, Woll PJ. Anti-angiogenic therapies for the treatment of angiosarcoma: a clinical update. Memo. 2017; 10(4): 190–193, doi: 10.1007/s12254-017-0365-x, indexed in Pubmed: 29250195.
52. Ray-Coquard IL, Domont J, Tresch-Bruneel E, et al. Paclitaxel Given Once Per Week With or Without Bevacizumab in Patients With Advanced Angiosarcoma: A Randomized Phase II Trial. J Clin Oncol. 2015; 33(25): 2797–2802, doi: 10.1200/JCO.2015.60.8505, indexed in Pubmed: 26215950.
53. D'Adamo DR, Dickson MA, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009; 27(19): 3133–3140, doi: 10.1200/JCO.2008.20.4495, indexed in Pubmed: 19451436.
54. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009; 27(19): 3126–3132, doi: 10.1200/JCO.2008.21.3223, indexed in Pubmed: 19451427.
55. Jagiełło-Wieczorek E, Świtaj T, Jagielska B, et al. Pazopanib as new therapeutic option in therapy of advanced soft tissue sarcoma. Onkol. Prak. Klin. 2014; 10: 24–31.

VIA MEDICA

CASE REPORT

Marcin J. Napierała[1], Anna M. Czarnecka[1, 2]

[1]Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Sklodowska-Curie Institute — Oncology Center in Warsaw, Poland
[2]Department of Experimental Pharmacology, Mossakowski Medical Research Centre,
Polish Academy of Sciences, Warsaw, Poland

Mucosal melanoma — clinical presentation and treatment based on a case series

Address for correspondence:
Lek. Marcin J. Napierała
Klinika Nowotworów Tkanek Miękkich,
Kości i Czerniaków
Centrum Onkologii — Instytut
im. Marii Skłodowskiej-Curie
ul. Roentgena 5, 02–781 Warszawa
Phone: +48 22 546 21 84
Fax: +48 22 643 93 75
e-mail: Marcin.Napierala@coi.pl

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 223–230
DOI: 10.5603/OCP.2019.0001
Translation: dr Elżbieta Stelmaszczyk

ISSN 2450–1654

ABSTRACT

Melanoma is malignant disease originating from melanocytes (pigment cells that occur mainly in the skin and constitute a type of defence from ultraviolet radiation). Melanocytes also occur outside of the skin (among others — in the eyeball, the mucosal lining of the digestive tract from the oral cavity to the anus, the nasal cavity and the paranasal sinuses, and the urinary and reproductive tracts). Many known cases of melanoma in the aforementioned locations exist.

The main factor responsible for the development of skin melanoma is ultraviolet radiation. In the case of mucosal melanoma, aetiological factors are still unknown. Mucosal melanoma most often develops in places that are hidden and not accessible through standard testing. Therefore, the disease develops without any signs for a long period of time before the proper diagnosis is established (usually at a disseminated stage, at a point where no successful localised treatment can be applied), which, in combination with a more aggressive course in comparison to more typical locations (the skin, the eyeball), a different sensitivity to systemic treatment (usually the lack of a mutation in the *BRAF* gene), and the lack of a separate standardised treatment procedure, is the cause of worse outcomes and poor prognosis.

Mucosal melanomas occur very rarely (about 1.5 % of all melanomas); however, the knowledge that a melanoma may also develop in locations that are often omitted during routine examination (the anus, the oral cavity, the urogenital region), may increase the chances of early diagnosis and attaining better treatment results.

In this paper, a brief description of the characteristics of mucosal melanoma is presented, along with a presentation of the most common locations, symptoms, diagnostic possibilities, and available treatment (including immunotherapy). Based on the available literature and personal experience, several cases of patients treated in the Institute of Oncology are described.

Key words: mucosal melanoma, mucosal melanoma treatment, nivolumab, pembrolizumab, ipilimumab

Oncol Clin Pract 2019; 15, 4: 223–230

Introduction

Melanocytes — cells that produce melanin — occur in the basal layer of the skin, the uvea, the arachnoid mater, and pia mater, but can also be found in the mucosal lining of the airways, digestive and urogenital tracts. Due to the presence of melanocytes mucosal melanoma may develop in all of the aforementioned locations. Mucosal melanoma is very rare, constituting only 0.03% of all neoplasms, and about 1.5% of all cases of melanoma [1–3]. While melanoma can develop on the surface of all mucosa, the majority occur in the mucosa of the head and neck (31–55%), the anus and rectum (17–24%), and the vulva and vagina (18–40%); the less common locations are the mucosal lining of the pharynx, larynx, urinary tract, uterine cervix, oesophagus, and gallbladder [3, 4]. It is noted, however, that a certain fraction of mucosal melanoma patients may be the ones who could

not have a primary lesion identified, and individuals with a skin melanoma that has undergone regression.

The incidence of skin melanoma has been rising — also in Poland — in the past two decades, while remaining stable in the case of mucosal melanoma [5, 6]. The risk of developing mucosal melanoma rises with age, and most of the patients are over 60 years of age (median age of diagnosis is 70 years). The incidence of mucosal melanoma is only twice as high in Caucasian individuals as in the African American population, while in the case of skin melanoma, this ratio is 16 to 1 [7]. Skin melanoma occurs more often in men than it does in women, and the frequency of occurrence of mucosal melanoma is 87% higher in women than it is in men, which is probably related to a greater percentage of melanoma of the reproductive organs in women [3].

Melanomas of the mucosa are characterised by a more aggressive course, and patients have a worse prognosis when compared to other types of melanoma (skin and ocular melanoma). The overall five-year survival rate for skin melanoma amounts to 80%, while for mucosal melanoma it only reaches 25%. The poorer treatment outcomes and shorter survival rate may be related to a generally more advanced disease upon diagnosis, anatomical factors that hinder complete resection and ample lymphatic drainage from the surfaces of mucosa, and other genetic and biological factors. The lack of early symptoms, and a sneaky evolution in locations that are typically inaccessible to examination, cause mucosal melanomas to be diagnosed late, at a time when the disease is very advanced. Amelanotic forms, which are not rare in the case of mucosal melanomas, additionally make the diagnosis more difficult. What is interesting, besides a lower survival rate since diagnosis, mucosal melanoma patients also have lower survival rates regardless of the stage of the disease, which especially pertains to people with metastases (M1 parameter) [3].

In mucosal melanoma patients, metastases are most often observed in the lungs (54%), liver (35%), and bones (25%) — the arrangement of metastasis locations differs from the case of skin melanoma, where metastases are found mainly in the skin (13–38%), lungs (18–36%), and lymph nodes (5–34%) [8].

Currently, there are no known risk factors for the development of mucosal melanoma. No relationship with ultraviolet radiation has been proven, and viral aetiology has also been excluded (within it — a relationship with SMV, EBV, HPV, or HSV) [9–11]. However, a greater percentage of individuals with history of formaldehyde exposure develop mucosal melanoma, as well as those who smoke tobacco (melanoma of the oral cavity), which may indicate the mutagenic effect of these two factors as well as an influence on the development of the illness [3, 7, 12, 13].

The types of molecular disorders responsible for the development of skin and mucosal melanoma differ from each other. In the case of skin melanoma, mutations in the *BRAF* gene occur in about half of the patients, while in the case of mucosal melanoma this mutation was identified in only a small number of patients (3–11% mucosal melanomas have the *BRAF* gene mutation, and another 5–14% have a mutation in the *NRAS* gene). However, the percentage of mutations occurring in the gene responsible for coding the receptor for tyrosine kinase (*KIT*) is greater. This mutation was identified in around 39% of mucosal melanoma patients, and 20% of rectal melanomas have deactivating mutations in the *NF1* gene [14–16]. Mucosal melanomas contain an average of 8193 point mutations per tumour, which is over 10 times fewer mutations than skin melanoma (86,495 changes). While gene amplifications are rare in skin melanoma, they are present in about 85% of mucosal melanomas. Furthermore, the mucosal melanoma has an average of 3.7 more structural variants when compared to the skin melanoma, and the cause of this increased chromosomal instability has not yet been explained [3].

Due to the rarity of its occurrence, the mucosal melanoma's aetiopathogenesis and clinical course are poorly known, and there is a lack of separate, specific recommendations pertaining to treatment, although the ESMO (European Society of Medical Oncology) and NCCN (National Comprehensive Cancer Network) recommendations point out the importance of radiotherapy in this group of patients [17].

In the process of diagnosing mucosal melanomas, it is crucial to rule out metastatic disease from a different location (primary lesion in the skin or eyeball), which means a thorough examination of the entire skin and mucosa, including a dental, ophthalmological, rectal, and gynaecological examination.

The main treatment method for patients who develop mucosal melanoma is surgical treatment. Unfortunately, due to its sneaky evolution and late diagnosis at a usually advanced stage, the results of surgical treatment are not satisfactory. A further limit to the precision of a resection is the location, which significantly defines the attainable surgical margin (the maxillary sinus, the rectal canal). In the treatment of mucosal melanomas, a relatively wide scope of resections was applied (i.e. abdominoperineal rectal resection in the case of anal cancer); however, long-term analyses show that long-term effects are not better when compared to a local excision with a wide margin, while the quality of life of the former patients is incomparably worse. Because of this, a wide local excision of the primary lesion is currently recommended, regardless of location, instead of a more extensive and debilitating operation. Radiotherapy improves localised control of the lesion

but does not affect the improvement of overall survival (OS). Currently there is no effective systemic treatment for this group of patients, and the results of treatment for mucosal melanoma in comparison with skin melanoma are clearly worse [18], which justifies the search for new methods.

Case reports

Case 1

A 56-year-old female came to the regional centre in May of 2017 due to swelling of the right side of her face. The patient was hospitalised in August 2017 in the department of otorhinolaryngology (ORL) in a voivodeship-level hospital for diagnostic purposes pertaining a tumour of the right nasal cavity — a biopsy was taken from the right maxillary sinus, and a partial resection of the lesion (R1) was performed; the pathology result established a diagnosis of melanoma. During another hospitalisation in a regional ORL department, a computed tomography (CT) imaging of the sinuses was performed, and showed an abnormal mass within the entire right maxillary and frontal sinuses, the right ethmoid sinus, and the right chamber of the sphenoid sinus, with an occlusion of the outflow tracts. The masses filled the nasal cavity on the right, with an infiltration of the right levator anguli oris, and a partial destruction of the cavity's medial wall the ethmoid bone. After several weeks, the patient underwent her first consultation at Centrum Onkologii — Instytut (COI) in Warsaw, and during the diagnostic process no mutation in the V600 codon of the *BRAF* gene was detected.

In December of 2017, immunotherapy (nivolumab — drug program) was initiated. As a continuation of local treatment, due to persistent bleeding from the lesion, the right external carotid artery was ligated, and a total maxillectomy with orbital exenteration was performed (R1 resection — February 2018). After surgery, the patient underwent adjuvant radiotherapy (May 2018) on the postoperative site up to a total dose of 5500 cGy/t. Immunotherapy was continued. In a control CT scan in September 2018, a suspicious lesion in the postoperative area was described, as well as lesions in the bronchi. The small tumour in the vicinity of the zygomatic bone in the postoperative lesions had a diameter of approximately 11 mm (previously 19 × 14 mm) and was not enhanced by contrast. The patient had a thin-needle biopsy of the lesion performed three times; no malignant cells were discovered. A 15 × 9 mm focal lesion on the right side of the trachea appeared, as well as a 6 mm lesion in the proximal section of the left bronchus, and an 11 mm lesion in the lower right lobar bronchus.

In March of 2018 the patient had a bronchoscopy with tissue sampling for the purpose of pathological testing — melanoma cells were detected in the sample tissue. The patient was referred to radiation oncologist to be qualified for brachytherapy. The patient remains in an overall adequate state. Due to the extensive surgery in the maxillofacial region, she has problems with speech. Laboratory tests show no significant abnormalities besides normocytic anaemia. The patient continues immunotherapy with no significant toxicity and no further disease progression.

Case 2

A 66-year-old male presented to the regional centre complaining of abnormal defecation pattern. Magnetic resonance imaging (MRI) of the pelvis performed in October 2017 described a cauliflower-like tumour mass in the lesser pelvic cavity sized 85 × 100 mm infiltrating subcutaneous tissue of the coccygeal region. A cutting needle biopsy (CNB) of the anal tumour was performed, showing a melanoma (*melanoma malignum* Melan A+, S-100 –/+). During the diagnostic process at COI, no distant metastases were described in the imaging, and a lack of the *BRAF B600* mutation was confirmed. Immunotherapy (pembrolizumab) was given within a drug program. In February 2018 the patient underwent radiotherapy of the rectum and lymph nodes with a dose up to 2500 cGy. In the most recent control CT (March of 2018), a tumourous mass was apparent, encompassing the anus and prostate, with stable dimensions and constant, transverse infiltration with dimensions of 61 × 43 mm, as well as lymph nodes of stable dimensions (a 12 mm lymph node by the right external iliac vessels, a 14 mm node by the right internal iliac vessels, and a node by the left external iliac vessels with 10 mm in the short axis). No metastases have been found so far. The patient remains in good general condition, with pain well controlled with analgesics. The disease has been stable for a year, and the immunotherapy has had the side effect of joint pain and skin pruritus assessed as level 1.

Case 3

A 65-year-old female presented to her regional gynaecology clinic due to vaginal bleeding. History included hypertension, asthma, and 20 years of cigarette smoking. In July 2018 an in-hospital biopsy of a vaginal lump was performed, and an initial diagnosis of a vaginal polyp was made. However, the results of pathology testing contained the diagnosis of a non-pigmented mucosal melanoma [CK(–), S100(+), HMB45(+)]. In a CT scan of the thorax, abdomen, and pelvis performed in 2018 no metastases were found (including any metastases to the lesser pelvis). In September 2018,

the patient underwent her first consultation at COI. Gynaecological examination showed an abnormal lesion about 2 cm in diameter in the vaginal wall, near the urethral opening, with a suspicion of infiltration of its distal part. In a CT of the thorax, abdomen, and pelvis performed in September 2018, the uterine body was smooth, free, ante-flexed, and with no pathological mass within the projection of the adnexa. Additionally, clinical examination revealed enlarged right inguinal lymph nodes.

Then, in October 2018, the patient underwent an excision of the exophytic lesion along with the distal part of the urethra (about 1 cm). Pathology results revealed infiltration of the mucosa and muscle layer of the urethra. The melanoma was 20% necrotic, and its greatest dimension was about 1.4 cm. The infiltration encompassed the mucosa and muscle layer of an ulcerated urethral wall. Neoplastic invasion of vessels was noted. No neoplastic invasion of the nerve fibres was revealed. Malignant infiltration was present in the front margin (R1), while other margins were free. The patient was referred for qualification for immunotherapy with immune checkpoint inhibitors and is currently being qualified for a clinical study.

Discussion

Mucosal melanoma immunotherapy

Current data on the effectiveness of checkpoint inhibitors is limited in the case of patients with mucosal melanoma. Several institutions have published analyses of patients with the diagnosis of mucosal melanoma, who were undergoing immunotherapy. The percentage of objective responses was, however, low (11.8%), although permanent responses were noted (including a permanent response to ipilimumab used as first-line treatment, and pembrolizumab as the second line). With a median observation time of 10.1 months, the median progression-free survival (PFS) and overall survival (OS) were 3.1 and 8.8 months, respectively. Nevertheless, amongst the scant number of patients who achieved objective responses, survival exceeding 56 months was observed [19]. In a comparative analysis of anti-PD-1 and anti-CTLA-4 treatment, a higher effectiveness of anti-PD-1 drugs was shown. In a French analysis, a total of 110 patients were included in the study. The median PFS was somewhat better in the group that received anti-PD1 drugs, when compared to the anti-CTLA4 group (3.9 months, compared with 2.9 months, P = 0.025) [20]. Single series of cases from other institutions revealed a complete lack of objective responses to anti-PD-1 treatment [21], although in other reports, the objective responses were seen in 23% of patients suffering from mucosal melanoma (median PFS — 3.9 months) [22].

The results of immune checkpoint inhibitor-based immunotherapy as monotherapy in patients with mucosal melanoma seem to be only somewhat better than known outcomes of chemotherapy. In the largest analysis of 95 patients undergoing chemotherapy due to mucosal melanomas, the median OS amounted to 12.1 months with the response rate of 26.3%. The results of this analysis were comparable to historical case series, and no statistical difference was revealed in the scope of responses between skin melanoma and mucosal melanoma (30% and 20%, P = 0.206); similarly, no difference was shown between patients of Caucasian and African origin (20% and 36%, respectively), and the median PFS in subsequent patient series amounted to 3 to 10 months [23].

The earliest results of immunotherapy are those from ipilimumab treatment (an anti-CTLA-4 drug). A retrospective analysis of 33 patients, most of whom were treated earlier at least once, showed a complete response in one patient, a partial response also in one patient, and six patients with stable disease according to the iRECIST immunological response criteria. The median OS from the time of the first dose of ipilimumab was 6.4 months (range: 1.8–26.7 months) [24].

Another analysis of 71 patients with metastatic mucosal melanoma treated with ipilimumab in an expanded access program in Italy showed an objective responses in 12% of patients, and a disease control rate of 36%, with a median observation time of 21.8 months. The average PFS in this patient group was 4.3 months, and the median OS reached 6.4 months [25].

In another study, which included patients with mucosal melanoma, seven patients were assessed, of whom only four completed the induction phase of four cycles of ipilimumab. One-year OS in this study was 14% and all patients with mucosal melanoma died within 24 months after receiving the first dose of ipilimumab. Of the patients studied, one achieved partial response, and two achieved stabilisation of disease [26]. The median OS, which amounted to 10.1 and 11.2 months, achieved by patients in the drug registration studies for ipilimumab, seems to be longer in comparison with the median OS found in smaller studies (6.4, 6.7, and 5.8 months, respectively) [24, 25, 27]. Ipilimumab treatment in conjunction with radiotherapy was also used in neoadjuvant treatment at the Memorial Sloan Kettering Cancer Centre. After applying such treatment, an R0 resection proved to be possible, as well as a single pathological response [28].

It has been shown that monoclonal antibodies aimed at PD-1 or PD-L1 are more effective, when compared with ipilimumab, in the treatment of melanoma patients, which suggested greater effectiveness in the treatment of

mucosal melanoma. The effectiveness of anti-PD1 antibodies in mucosal melanoma patients has so far been fairly well documented. The effectiveness of pembrolizumab treatment was tested based on data from registration studies. Of the patients treated in the studies of KEYNOTE-001 (NCT01295827), -002 (NCT01704287), and -006 (NCT01866319), 84 (5%) were treated for a diagnosis of mucosal melanoma. Fifty-one of 84 patients did not receive earlier ipilimumab immunotherapy. In patients with a diagnosis of mucosal melanoma, the objective response rate was 19%, and the median response duration was 27.6 months. Responses were achieved in 22% of patients not treated with ipilimumab, and in 15% of those who were treated with this drug as the first line of treatment. The average PFS amounted to 2.8 months, and the median OS reached 11.3 months [29].

The first interesting case of response to nivolumab immunotherapy in a patient with mucosal melanoma was reported in the CheckMate 066 study. A case of a patient with an untreated metastatic mucosal melanoma was described, with high initial lactate dehydrogenase (LDH) activity (seven-times the upper reference limit). The patient was included into a clinical trial, achieving partial response and subsequently permanent total response. LDH activity decreased significantly within two months of the beginning of treatment (at which time the patient achieved partial response) and was maintained at a low level throughout the observation period. The patient suffered only mild side effects (levels 1–2: vitiligo and skin rash).

The research team suggested that nivolumab treatment may be considered in mucosal melanoma patients with high LDH activity [30]. In order to evaluate the effectiveness of nivolumab in patients with a diagnosis of mucosal melanoma, a phase III study analysis was conducted. In 86 patients with mucosal melanoma, who were treated in clinical trials, the percentage of objective responses amounted to 23.3% for nivolumab as monotherapy, and 37.1% in the group treated with nivolumab combined with ipilimumab. The average PFS was 3.0 months for patients treated with nivolumab monotherapy, and 5.9 months for those receiving nivolumab plus ipilimumab, which suggests that nivolumab in combination with ipilimumab has greater effectiveness than any one of these drugs given as monotherapy [31]. An interesting fact is that the expression of PD-L1 in skin and mucosal melanoma patients was different; fewer patients with mucosal melanoma were PD-L1 positive (17.4% and 28.6% with a 5% PD-L1 expression in the group receiving nivolumab monotherapy and the group receiving combination therapy, respectively). In skin melanoma patients, this percentage was 34.3% and 36.8%, with 5% having PD-L1 expression in monotherapy and combined therapy. The rates of treatment response were higher in the group of mucosal melanoma patients with a greater than 5% PD-L1 expression, although responses were still observed in the < 5% PD-L1 expression group, both in those receiving monotherapy as well as nivolumab with ipilimumab [31].

Sequential treatment in mucosal melanoma patients was evaluated in Japanese institutions. Out of 60 patients, only 38% finished treatment with four doses of ipilimumab. Objective response was achieved in the second-line of immunotherapy in 3.6% of patients. Side effects associated with immunotherapy occurred in 78% of the patients, and 70% of them had level 3 and 4 side effects, where 31% of patients had two or more side effects. A time less than 28 days between the first- and second-lines of treatment correlated with the development of immunological complications [32].

New treatment methods for mucosal melanoma include combinations of immunotherapies, or immunotherapies and local therapies. Single examples of effective peritumoral injections with β-interferon (IFN-β) and interleukin 2 (IL-2) in combination with nivolumab have been reported [33, 34]. Targeted treatment, including that with the use of BRAF/MEK or KIT inhibitors (imatinib), may be considered in the carriers of adequate mutations [35].

Mucosal melanoma of the oral cavity

The diagnostic criteria for primary oral cavity mucosal melanoma include the appearance of a clinical and microscopic presentation of a neoplasm in the mucosa of the oral cavity, the presence of melanocytic proliferative nests in the mucosa of the oral cavity, and failure to establish a different primary location [36, 37]. Considering the fact that 1/3 of oral mucosal melanoma cases develop from previously existing melanotic lesions, every abnormalities in the area are worth assessing, and an excisional biopsy should be performed in doubtful situations. Excision still remains the main treatment method, which is combined with adjuvant radiotherapy, and immuno/chemotherapy. These melanomas are characterised by several features:

— they usually develop de novo; however, in 1/3 of cases they develop from a previous melanotic lesion [38, 39];
— initially the tumour is usually symptom-less, with the appearance of a flat mark or slightly raised, irregular melanotic lesion [40, 41];
— at a later stage of the disease, swelling, ulceration, bleeding, and pain appear, with the possibility of dental mobility, and the primary lesion becomes raised and lumpy
— the primary lesion may develop satellite lesions [42];
— amelanotic types of melanoma in the oral cavity are not rare, they usually delay diagnosis and treatment, and consequently have a worse prognosis [43];

— in about 25% of patients, metastases to the regional lymph nodes are present at the time of diagnosis [40, 41];
— 5-year survival rate is poor, at 12.3–16.6%, with a median survival of 2 years [38, 44].

Melanoma of the colon and anal mucosa

Melanoma of the anorectal region is often initially misdiagnosed as haemorrhoids, which significantly delays the proper diagnosis, and worsens patient prognosis. Most melanomas in this area are localised within the reach of the *per rectum* examination, which, in most cases, enables them to recognise any abnormalities. Unfortunately, even 1/3 of anorectal melanomas are amelanotic, and a biopsy of the lesion is key in the diagnosis of a suspicious lesion. The Miles operation (an abdominoperineal resection in anorectal melanoma) was considered the standard treatment for melanoma in this location. Currently, it seems that wide local excision will take its place. While a less invasive treatment, it gives similar long-term results. A wide local excision provides more local remissions, but does not affect the OS rate, and adjuvant radiotherapy improves local maintenance but does not affect survival [45–48]. The five-year survival rate for locally advanced disease is 26.7%, and 9.8% for disease with metastases to lymph nodes, with a median OS of 24 months and 17 months, respectively. In patients with metastases to the lymph nodes, a selective lymphadenectomy is recommended [49]. Additionally, the melanoma in this particular area:
— is the most common primary site of melanoma of the digestive tract mucosa [50];
— is the third most common location after skin and ocular melanoma [50];
— melanoma of the ano-rectal region occurs most often in patients 65–70 years of age, with women in the lead [45, 49];
— the primal lesion may occur in the anal canal, the rectum, or in both of these places;
— in most cases it occurs within 6 cm of the anal verge [51];
— the most common symptoms are: anal bleeding, pain and discomfort in the anal region, as well as anal prolapse of the tumour [2];
— amelanotic tumours constitute about 30% of cases [2];
— non-specific symptomatology, polymorphism of the primary site often influence a wrong primary diagnosis — this pertains to about 2/3 of patients (most often diagnosed as haemorrhoids, adenocarcinoma, polyps, rectal cancer) [46, 51];
— at time of diagnosis, 30% of patients already has metastases (regional or distant) [45, 52];
— overall survival remains poor (20% after 5 years with median survival of 14–20 months) [18, 51, 53].

Melanoma of the genitourinary system

Genito-urinary melanomas are rare and can develop from the mucosa of any part of the genitourinary tract (the vulva, vagina, cervix, urethra, bladder). Women are affected more often. Following features are characteristic of these melanomas:
— melanoma developing from the female genital tract constitutes 18% of all cases of mucosal melanoma and most often pertains to the vulva (76.7%) and vagina (19.8%) [2, 39];
— vulvar melanoma usually affects women around 68 years of age, mainly Caucasian (90%), and develops around the clitoris and labia majora [54];
— the main symptoms of vulvar melanoma include: bleeding, lumpy lesions or a thickening on the vulva, pruritus, pain, inflammation, pain during urination, discharge [55, 56];
— the main treatment method for vulvar melanoma is surgical excision, and, similarly to the previously described forms of mucosal melanoma, a more conserving surgery is recommended due to a lack of difference in survival [57].

Melanoma of the airways

Melanomas of the airway mucosa are most often located in the nasal cavity and the paranasal sinuses, and the tumour can also be amelanotic. They are characterised with the following features:
— the most common symptoms include: unilateral obstruction of the nasal cavity, pathological tissue mass, nasal bleeding [58];
— at a more advances stage: pain, facial deformation, less often exophthalmos double vision;
— macroscopically the tumour has the appearance of a multi-shaped brown or black mass, often ulcerated;
— 5-year survival rate for melanoma of the nasal cavity is 31%, and 0% for melanoma of the maxillary sinus [44].

Summary

Awareness of the possibility for melanoma occuring in places that are available for examination (i.e. the oral cavity, urogenital region, anal canal) allows for a diagnosis of the disease at an early stage, which gives an opportunity for better treatment outcomes. A diagnosis of the disease at a point of dissemination, which is unfortunately when mucosal melanoma is most frequently diagnosed, is still predictive of a very unfavourable outcome, and the results of systemic treatment are poor. The presented cases show that immunotherapy can be an effective method of treatment for patients

with metastatic mucosal melanoma, although generally mucosal melanomas have poorer outcomes when compared with skin melanoma (shorter PFS and OS) when it comes to treatment with nivolumab, or pembrolizumab in monotherapy. Some patients may benefit significantly from immunotherapy, especially combination of anti-PD-1 with anti-CTLA-4, but currently we have no legitimate predictive biomarkers for patient selection. Despite many effective treatment options for skin melanoma, data on the treatment of melanomas in other locations are limited, and clinical decisions are often made based on retrospective data and reports from other institutions, including case series analyses.

References

1. Topić B, Mašić T, Radović S, et al. Primary Oral Mucosal Melanomas — Two Case Reports and Comprehensive Literature Review. Acta Clin Croat. 2017; 56(2): 323–330, doi: 0.20471/acc.2017.56.02.17, indexed in Pubmed: 29485801.
2. Mihajlovic M, Vlajkovic S, Jovanovic P, et al. Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol. 2012; 5(8): 739–753, indexed in Pubmed: 23071856.
3. Lerner BA, Stewart LA, Horowitz DP, et al. Mucosal Melanoma: New Insights and Therapeutic Options for a Unique and Aggressive Disease. Oncology (Williston Park). 2017; 31(11): e23–e32, indexed in Pubmed: 29179253.
4. Werdin C, Limas C, Knodell R. Primary malignant melanoma of the rectum. Evidence for origination from rectal mucosal melanocytes. Cancer. 1988; 61(7): 1364–1370, doi: 10.1002/1097-0142(19880401)61:7<1364::aid-cncr2820610715>3.0.co;2-b.
5. Taneja SS. Re: Cancers with increasing incidence trends in the United States: 1999 through 2008. J Urol. 2012; 188(4): 1120–1121, doi: 10.1016/j.juro.2012.06.090, indexed in Pubmed: 22971362.
6. Simard EP, Ward EM, Siegel R, et al. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin. 2012; 62(2): 118–128, doi: 10.3322/caac.20141, indexed in Pubmed: 22281605.
7. Yde SS, Sjoegren P, Heje M, et al. Mucosal Melanoma: a Literature Review. Curr Oncol Rep. 2018; 20(3): 28, doi: 10.1007/s11912-018-0675-0, indexed in Pubmed: 29569184.
8. DeMatos P, Tyler DS, Seigler HF. Malignant melanoma of the mucous membranes: a review of 119 cases. Ann Surg Oncol. 1998; 5(8): 733–742, indexed in Pubmed: 9869521.
9. Dahlgren L, Schedvins K, Kanter-Lewensohn L, et al. Human papilloma virus (HPV) is rarely detected in malignant melanomas of sun sheltered mucosal membranes. Acta Oncol. 2005; 44(7): 694–699, doi: 10.1080/02841860500247461, indexed in Pubmed: 16227159.
10. Lundberg R, et al. Human herpes virus DNA is rarely detected in non-UV light-associated primary malignant melanomas of mucous membranes. Anticancer Res. 2006; 26(5B): 3627–3631.
11. Giraud G, Ramqvist T, Ragnarsson-Olding B, et al. DNA from BK virus and JC virus and from KI, WU, and MC polyomaviruses as well as from simian virus 40 is not detected in non-UV-light-associated primary malignant melanomas of mucous membranes. J Clin Microbiol. 2008; 46(11): 3595–3598, doi: 10.1128/JCM.01635-08, indexed in Pubmed: 18768658.
12. Holmstrom M, Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. Occupational and Environmental Medicine. 1991; 48(1): 9–11, doi: 10.1136/oem.48.1.9.
13. AXEIX T, HEDIN C. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. European Journal of Oral Sciences. 1982; 90(6): 434–442, doi: 10.1111/j.1600-0722.1982.tb00760.x.
14. Purdue MP. Re: Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst. 2005; 97(5): 401–2; author reply 402, doi: 10.1093/jnci/dji074, indexed in Pubmed: 15741578.
15. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst. 2003; 95(24): 1878–1890, indexed in Pubmed: 14679157.
16. Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006; 24(26): 4340–4346, doi: 10.1200/JCO.2006.06.2984, indexed in Pubmed: 16908931.
17. Pittaka M, Kardamakis D, Spyropoulou D. Comparison of International Guidelines on Mucosal Melanoma of the Head and Neck: A Comprehensive Review of the Role of Radiation Therapy. In Vivo. 2016; 30(3): 165–170.
18. Chang A, Karnell L, Menck H. The National Cancer Data Base report on cutaneous and noncutaneous melanoma. Cancer. 1998; 83(8): 1664–1678, doi: 10.1002/(sici)1097-0142(19981015)83:8<1664::aid-cncr23>3.0.co;2-g.
19. Kuo JC. Immune checkpoint inhibitors in the treatment of advanced mucosal melanoma. Melanoma Manag. 2017; 4(3): 161–167, doi: 10.2217/mmt-2017-0014, indexed in Pubmed: 30190921.
20. Taquin H, Fontas E, Massol O, et al. Efficacy and safety data for checkpoint inhibitors in advanced melanoma under real-life conditions: A monocentric study conducted in Nice from 2010 to 2016. Ann Dermatol Venereol. 2018; 145(11): 649–658, doi: 10.1016/j.annder.2018.06.008, indexed in Pubmed: 30098818.
21. Thierauf J, Veit JA, Hess J, et al. Checkpoint inhibition for advanced mucosal melanoma. Eur J Dermatol. 2017; 27(2): 160–165, doi: 10.1684/ejd.2016.2949, indexed in Pubmed: 28174141.
22. Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer. 2016; 122(21): 3354–3362, doi: 10.1002/cncr.30259, indexed in Pubmed: 27533633.
23. Cui C, Tang B, Guo J. Chemotherapy, biochemotherapy and anti-VEGF therapy in metastatic mucosal melanoma. Chin Clin Oncol. 2014; 3(3): 36, doi: 10.3978/j.issn.2304-3865.2014.07.02, indexed in Pubmed: 25841462.
24. Postow MA, Luke JJ, Bluth MJ, et al. Ipilimumab for patients with advanced mucosal melanoma. Oncologist. 2013; 18(6): 726–732, doi: 10.1634/theoncologist.2012-0464, indexed in Pubmed: 23716015.
25. Del Vecchio M, Di Guardo L, Ascierto PA, et al. Efficacy and safety of ipilimumab 3mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer. 2014; 50(1): 121–127, doi: 10.1016/j.ejca.2013.09.007, indexed in Pubmed: 24100024.
26. Zimmer L, Eigentler TK, Kiecker F, et al. Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med. 2015; 13: 351, doi: 10.1186/s12967-015-0716-5, indexed in Pubmed: 26541511.
27. Alexander M, Mellor JD, McArthur G, et al. Ipilimumab in pretreated patients with unresectable or metastatic cutaneous, uveal and mucosal melanoma. Med J Aust. 2014; 201(1): 49–53, indexed in Pubmed: 24999899.
28. Schiavone MB, Broach V, Shoushtari AN, et al. Combined immunotherapy and radiation for treatment of mucosal melanomas of the lower genital tract. Gynecol Oncol Rep. 2016; 16: 42–46, doi: 10.1016/j.gore.2016.04.001, indexed in Pubmed: 27331137.
29. Hamid O, Robert C, Ribas A, et al. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br J Cancer. 2018; 119(6): 670–674, doi: 10.1038/s41416-018-0207-6, indexed in Pubmed: 30202085.
30. Ascierto PA, Vanella V, Grimaldi AM, et al. Complete response to nivolumab monotherapy in a treatment-naive, BRAF wild-type patient with advanced mucosal melanoma and elevated lactate dehydrogenase: a case report from a phase III trial. Cancer Immunol Immunother. 2016; 65(11): 1395–1400, doi: 10.1007/s00262-016-1898-2, indexed in Pubmed: 27604993.
31. D'Angelo SP, Larkin J, Sosman JA, et al. Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis. J Clin Oncol. 2017; 35(2): 226–235, doi: 10.1200/JCO.2016.67.9258, indexed in Pubmed: 28056206.
32. Fujisawa Y, Yoshino K, Otsuka A, et al. Retrospective study of advanced melanoma patients treated with ipilimumab after nivolumab: Analysis of 60 Japanese patients. J Dermatol Sci. 2018; 89(1): 60–66, doi: 10.1016/j.jdermsci.2017.10.009, indexed in Pubmed: 29079332.
33. Fusumae T, Kamiya K, Chiang B, et al. Synergistic effects of interferon-beta and nivolumab in oral mucosal melanoma. J Dermatol. 2018; 45(1): 87–90, doi: 10.1111/1346-8138.14041, indexed in Pubmed: 28944501.
34. Heppt MV, Goldscheider I, Tietze JK, et al. Intralesional interleukin-2 for unresectable mucosal melanoma refractory to nivolumab. Cancer Immunol Immunother. 2017; 66(10): 1377–1378, doi: 10.1007/s00262-017-2012-0, indexed in Pubmed: 28497158.
35. Malaguarnera G, Madeddu R, Catania VE, et al. Anorectal mucosal melanoma. Oncotarget. 2018; 9(9): 8785–8800, doi: 10.18632/oncotarget.23835, indexed in Pubmed: 29492238.
36. Chidzonga MM, Mahomva L, Marimo C, et al. Primary malignant melanoma of the oral mucosa. J Oral Maxillofac Surg. 2007; 65(6):

1117–1120, doi: 10.1016/j.joms.2006.11.045, indexed in Pubmed: 17517294.
37. Greene GW, Haynes JW, Dozier M, et al. Primary malignant melanoma of the oral mucosa. Oral Surg Oral Med Oral Pathol. 1953; 6(12): 1435–1443, indexed in Pubmed: 13120118.
38. Hicks MJ, Flaitz CM. Oral mucosal melanoma: epidemiology and pathobiology. Oral Oncol. 2000; 36(2): 152–169, indexed in Pubmed: 10745167.
39. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. J Am Acad Dermatol. 2007; 56(5): 828–834, doi: 10.1016/j.jaad.2006.06.017, indexed in Pubmed: 17349716.
40. Borst A, Schwipper V. Primary mucosal malignant melanoma of the head and neck. Facial Plast Surg. 2011; 27(3): 237–242, doi: 10.1055/s-0031-1275772, indexed in Pubmed: 21567342.
41. Patel SG, Prasad ML, Escrig M, et al. Primary mucosal malignant melanoma of the head and neck. Head Neck. 2002; 24(3): 247–257, indexed in Pubmed: 11891956.
42. Devi P, Bhovi T, Jayaram RR, et al. Malignant melanoma of the oral cavity showing satellitism. J Oral Sci. 2011; 53(2): 239–244, indexed in Pubmed: 21712630.
43. Notani K, Shindoh M, Yamazaki Y, et al. Amelanotic malignant melanomas of the oral mucosa. Br J Oral Maxillofac Surg. 2002; 40(3): 195–200, doi: 10.1054/bjom.2001.0713, indexed in Pubmed: 12054708.
44. Manolidis S, Donald P. Malignant mucosal melanoma of the head and neck. Cancer. 1997; 80(8): 1373–1386, doi: 10.1002/(sici)1097-0142(19971015)80:8<1373::aid-cncr3>3.0.co;2-g.
45. Iddings DM, Fleisig AJ, Chen SL, et al. Practice patterns and outcomes for anorectal melanoma in the USA, reviewing three decades of treatment: is more extensive surgical resection beneficial in all patients? Ann Surg Oncol. 2010; 17(1): 40–44, doi: 10.1245/s10434-009-0705-0, indexed in Pubmed: 19774417.
46. Zhou, H.T., , Wide local excision could be considered as the initial treatment of primary anorectal malignant melanoma. Chin Med J (Engl), 2010. 123(5): p. : 585–8.
47. Yap LB, Neary P. A comparison of wide local excision with abdominoperineal resection in anorectal melanoma. Melanoma Res. 2004; 14(2): 147–150, indexed in Pubmed: 15057046.
48. Kelly P, Guadagnolo A, Cormier JN, et al. Sphincter-sparing Local Excision and Hypofractionated Radiation Therapy for Anal-rectal Melanoma: A 20 Year Experience. International Journal of Radiation Oncology*Biology*Physics. 2010; 78(3): S611–S612, doi: 10.1016/j.ijrobp.2010.07.1423.
49. Coté TR, Sobin LH. Primary melanomas of the esophagus and anorectum: epidemiologic comparison with melanoma of the skin. Melanoma Res. 2009; 19(1): 58–60, doi: 10.1097/CMR.0b013e32831ef262, indexed in Pubmed: 19430407.
50. Cheung MC, Perez EA, Molina MA, et al. Defining the role of surgery for primary gastrointestinal tract melanoma. J Gastrointest Surg. 2008; 12(4): 731–738, doi: 10.1007/s11605-007-0417-3, indexed in Pubmed: 18058185.
51. Zhang S, Gao F, Wan D. Effect of misdiagnosis on the prognosis of anorectal malignant melanoma. J Cancer Res Clin Oncol. 2010; 136(9): 1401–1405, doi: 10.1007/s00432-010-0793-z, indexed in Pubmed: 20130908.
52. Weyandt GH, Eggert AO, Houf M, et al. Anorectal melanoma: surgical management guidelines according to tumour thickness. British Journal of Cancer. 2003; 89(11): 2019–2022, doi: 10.1038/sj.bjc.6601409.
53. Liu G, Wang Y, Fei F, et al. Clinical characteristics and preliminary morphological observation of 47 cases of primary anorectal malignant melanomas. Melanoma Res. 2018; 28(6): 592–599, doi: 10.1097/CMR.0000000000000491, indexed in Pubmed: 30080746.
54. Sugiyama VE, Chan JK, Shin JY, et al. Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol. 2007; 110(2 Pt 1): 296–301, doi: 10.1097/01.AOG.0000271209.67461.91, indexed in Pubmed: 17666603.
55. Ragnarsson-Olding B, Nilsson B, Kanter-Lewensohn L, et al. Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females. Cancer. 1999; 86(7): 1285–1293, doi: 10.1002/(sici)1097-0142(19991001)86:7<1285::aid-cncr25>3.0.co;2-p.
56. Verschraegen CF, Benjapibal M, Supakarapongkul W, et al. Vulvar melanoma at the M. D. Anderson Cancer Center: 25 years later. Int J Gynecol Cancer. 2001; 11(5): 359–364, indexed in Pubmed: 11737466.
57. Piura B. Management of primary melanoma of the female urogenital tract. Lancet Oncol. 2008; 9(10): 973–981, doi: 10.1016/S1470-2045(08)70254-7, indexed in Pubmed: 19071254.
58. Thompson L, Wieneke J, Miettinen M. Sinonasal Tract and Nasopharyngeal Melanomas: A Clinicopathologic Study of 115 Cases With a Proposed Staging System. The American Journal of Surgical Pathology. 2003; 27(5): 594–611, doi: 10.1097/00000478-200305000-00004.

VIA MEDICA

CASE REPORT

Katarzyna Kryszczyszyn-Musialik[1, 2], Grzegorz Słomian[1], Krzysztof Musialik[3]

[1]Oncology Department, Provincial Specialist Hospital No. 3 in Rybnik, Poland
[2]Chair and Department of Medicine and Environmental Epidemiology, Medical University of Silesia in Katowice, Poland
[3]Trauma and Orthopaedic Department, Provincial Specialist Hospital No. 2 in Jastrzebie-Zdroj, Poland

Hodgkin's lymphoma with multifocal *Staphylococcus aureus* infection in a 29-year-old male — a case study

Address for correspondence:
Lek. Katarzyna Kryszczyszyn-Musialik
Oddział Onkologii, Wojewódzki
Szpital Specjalistyczny nr 3 w Rybniku
ul. Energetyków 46, 44–200 Rybnik
Phone: 32 429 17 60
e-mail: kryszczyszyn@gmail.com

Oncology in Clinical Practice
2019, Vol. 15, No. 4, 231–236
DOI: 10.5603/OCP.2019.0028
Translation: dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Hodgkin's lymphoma (HL) is a neoplastic disease of the lymphoid tissue. It is characterised by the presence of B lymphocyte-derived monoclonal Reed-Sternberg and Hodgkin cells, which tend to create a massive inflammation reaction in lymph nodes. Lymphadenopathy is common. The prognosis depends on the clinical stage according to Ann Arbor (Cotswold's modification) classification and unfavourable prognostic factors. The ABVD chemotherapy regimen is the gold standard of treatment for patients with HL. This case report presents a patient diagnosed and treated for neck presentation of Hodgkin's lymphoma intricate sepsis and coxarthritis because of *Staphylococcus aureus* infection. The treatment was arthrotomy. After the patient's recovery chemotherapy was continued and complete remission was achieved.

Key words: Hodgkin disease, hip joint, *Staphylococcus aureus*

Oncol Clin Pract 2019; 15, 4: 231–236

Introduction

Hodgkin's lymphoma (HL) is a malignancy of lymphoid tissue. It is characterised by the presence of B lymphocyte-derived monoclonal Reed-Sternberg cells and Hodgkin's cells, which induce a massive reaction of normal lymphocytes in the lymph nodes. Therefore, lymphadenopathy is a common clinical manifestation. In the microscopic image of affected lymph node, reactive cells predominate and cancerous cells constitute a minority — around 2% [1, 2]. The incidence of Hodgkin's lymphoma is constant, whilst the course of morbidity curve is bimodal, with two peaks at the age of 25–30 and 50–55 years [3]. In 2010, over 700 new cases were reported in Poland [3].

The prognosis in patients with HL depends on clinical stage (CS) of disease assessed according to the Ann Arbor classification and the presence of unfavourable prognostic factors [4, 5]. The ABVD chemotherapy regimen is the gold standard of the treatment for patients with HL [6]. In special cases, due to vital indications, such as: extremely rapid disease dynamics, superior vena cava syndrome (SVCS), compression of the spinal cord, compression of the airways with dyspnoea, or ureteral closure, it may be necessary to initiate the treatment before the diagnosis is completed [5]. All issues that cause delayed diagnosis, as well as implementation and continuation of optimal therapy, reduce the patient's chances to be cured. This paper describes a case of a patient of the Oncology Department with the Haematology Subdivision of Provincial Specialist Hospital No. 3 in Rybnik — a 29-year-old man diagnosed and treated for tumours and neck phlegmon with subsequent diagnosis of HL, complicated by acute respiratory failure, purulent infections of soft tissues, and blood-borne hip arthritis with septic shock in the course of *Staphylococcus aureus* infection.

Case report

According to an interview in January 2013, a 29-year-old man noticed clinical symptoms in the

form of a neck tumour located in the middle part and then covering the left side of the neck. In March 2013, the patient visited a family doctor who ordered an antibiotic — amoxicillin with clavulanic acid administered orally. Therapy did not bring the expected improvement. The patient observed intensification of the inflammatory process with the progression of infiltration to the chest and the formation of purulent fistula. The patient was admitted to the ENT department. A neck phlegmon penetrating into the mediastinum was diagnosed and antibiotic therapy with ceftriaxone and metronidazole was introduced. In a computed tomography (CT) examination of the neck and chest, a neck abscess penetrating into the mediastinum and cervical lymphadenopathy with compression and modelling of the trachea were described. The lesions raised the suspicion of a proliferative disease of the lymphatic system with secondary purulent lesions. The patient was referred for further treatment to the chest surgery clinic, where the neck and mediastinum were drained, and antibiotic therapy was continued according to the culture (imipenem). Then a mediastinoscopy was performed with a biopsy. The histopathological report described: "*Neoplasma malignum probabiliter lymphogenes*. Due to the small amount of material available for immunohistochemistry (predominant necrotic masses), its execution was abandoned, with a recommendation to carry it out in the oncological centre". The patient was advised to continue treatment in the oncology centre, and a consultation date was agreed.

On May 24, 2013 (before the date of consultation in the oncology centre), the patient was admitted to the Hospital Emergency Department of Provincial Specialistic Hospital No. 3 in Rybnik in a severe condition with symptoms of acute respiratory failure and SVCS. The patient was intubated, and a CT scan was performed (Fig. 1, 2) in which the airway pressure was visualised. The patient was admitted to the Intensive Care Unit (ICU), where sedation and mechanical ventilation were used. Due to the pressure of tumour masses on the respiratory tract, leading to respiratory failure, a decision was made to introduce antineoplastic treatment. In the initial histopathological examination, cancer originating from the lymphatic system was diagnosed. At the time of making the decision to start treatment with vital indications, there was no more precise diagnosis. High dynamics of the disease suggested aggressive lymphoma, as in diffuse large B-cell lymphoma (DLBCL). Based on these clinical data, the patient was qualified for CHOP chemotherapy.

In ICU the patient received one cycle of CHOP rescue chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone). Reduction in the swelling of neck tissues was achieved. The patient was disconnected

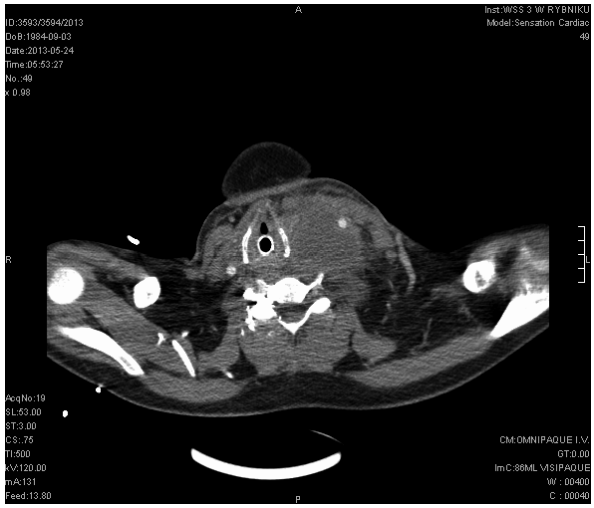

Figure 1. Computed tomography of the neck and chest before treatment. Extensive hypodense structures in the neck and mediastinum over a length of about 20 cm. The maximum cross-section of changes in the neck and mediastinum — 10 × 7.5 cm

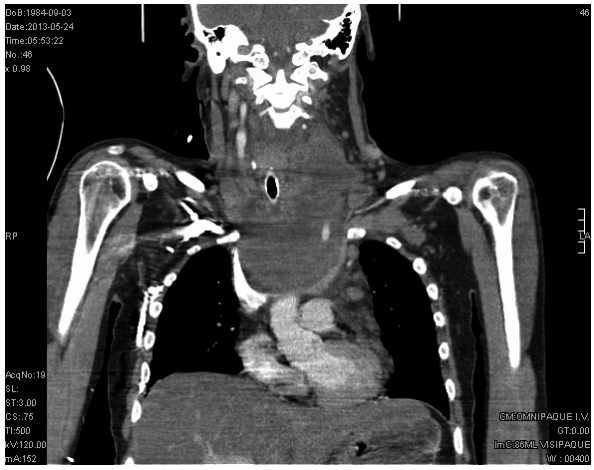

Figure 2. Computed tomography of the neck and chest before treatment. Larynx, thyroid, and oesophagus structures are compressed and displaced towards the right side; trachea modelled, compressed, with endotracheal tube in the lumen

from the ventilator and extubated. In order to protect the airway obstruction, a tracheostomy was performed.

After improving the general condition, the patient was transferred to the Oncology Department. At admission, the patient was in good performance status according to the ECOG (Eastern Cooperative Oncology Group) scale, scoring 2. During the stay, the second CHOP cycle was administered. In order to establish the diagnosis, histopathological verification and immunohistochemical examination were ordered. After the second cycle, the patient was discharged home.

Between the cycles, the patient was hospitalised in the Department of Internal Diseases due to inflammatory infiltration of both forearms with the formation of left forearm abscess in the course of staphylococcus infection, where antibiotic therapy according to the antibiogram was continued until the symptoms resolved (ciprofloxacin was administered parenterally).

During the next, third cycle of chemotherapy a verified histopathological diagnosis was given: "Classical Hodgkin's lymphoma [CD30(+), CD15(+), MUM1(+), CD20(–), CD3(–)]. Extensive necrotic changes present in the material make it impossible to determine the subtype". In order to determine the current clinical stage of the disease, imaging examinations were performed (Fig. 3–5), in which the reduction of infiltrative lesions was confirmed. Establishing the initial stage was very difficult because the patient started treatment in an ICU, without full diagnosis, and with no bone marrow trepanobiopsy or positron emission tomography (PET). On the basis of imaging (CT) and laboratory tests performed at the ICU, the disease clinical stage was assessed as IIB with the presence of unfavourable prognostic factors. In medical history the patient reported a decrease in body weight and recurrent fevers, so it was considered that general symptoms were also present. The patient was qualified for 6–8 cycles of ABVD chemotherapy followed by involved-field radiotherapy (IF-RT) at a dose of 20–36 Gy for residual or primary tumour [6]. ABVD chemotherapy was started. Due to the presence of additional risk factors for febrile neutropaenia (FN), such as advanced disease and poor general condition, the patient was qualified for FN primary prevention using short-acting granulocyte colony-stimulating factors (G-CSF). The patient continued chemotherapy in a good general condition, without significant complications.

On August 23, 2013, the patient was admitted for the fourth cycle of ABVD chemotherapy in severe general condition; ECOG performance status was defined as 3/4. The patient was lying due to the pain of the sacral and lumbar spine regions and lower limbs. In the physical examination the following were seen: forced abduction of lower limb, severe groin and right thigh pain, and right limb paresis with normal blood supply and innervation. The patient was suffering a lot despite intensive treatment — his pain intensity on the Numerical Rating Scale (NRS) was determined as 10. Laboratory tests revealed increased inflammation parameters (C-reactive protein [CRP] — 216.56 mg/L, erythrocyte sedimentation rate [ESR] — 110 mm/h).

A CT scan was performed in which the features of the right hip joint damage were shown (Fig. 6, 7). Based on clinical status and imaging examinations, haematogenous (blood-borne) hip arthritis was diagnosed. Broad-spectrum intravenous antibiotics were introduced: vancomycin at a dose of 1 g every 12 hours and cloxacillin 500 mg every 6 hours.

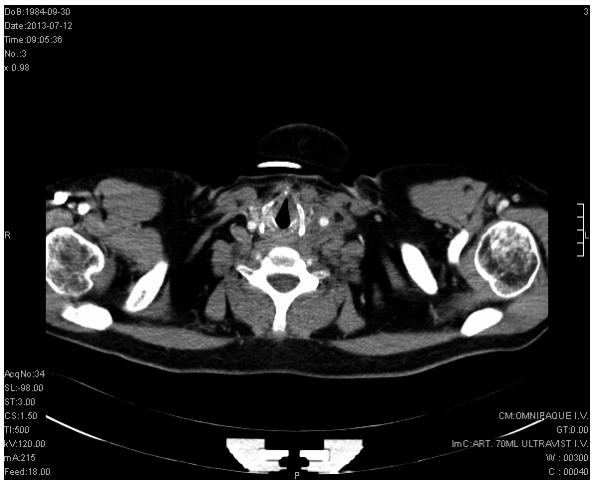

Figure 3. Computed tomography of the neck and chest before treatment. From the back the structure of infiltration reaches the paraspinal region with the width from approx. 7 cm

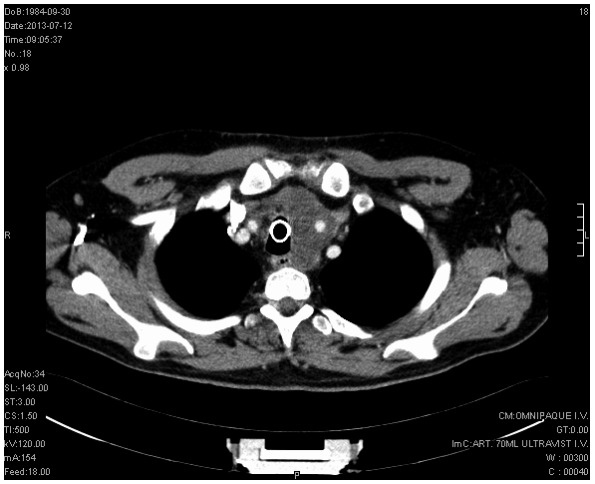

Figure 4. Computed tomography of the neck and chest after 2 cycles of chemotherapy. Currently, the pathological structure in the mediastinum and neck is much smaller than in the previous study

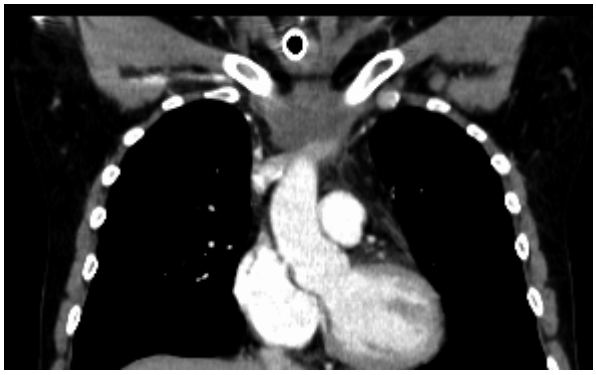

Figure 5. Computed tomography of the neck and chest after 2 cycles of chemotherapy. The largest dimensions of the lesion are 63 × 40 mm

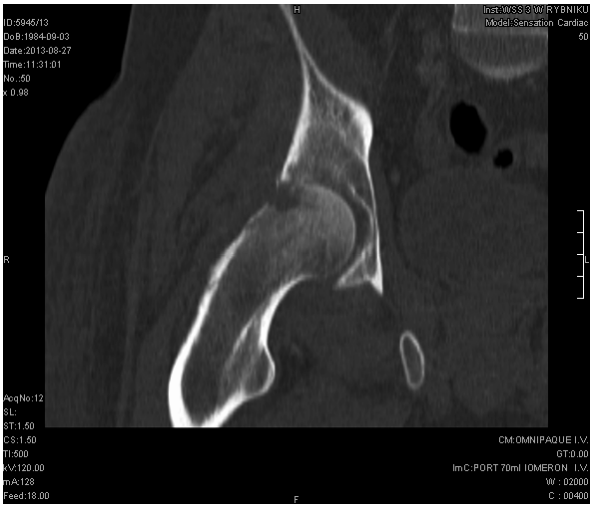

Figure 6. Computed tomography of the chest, abdomen, and pelvis; right hip joint. Interruption of the cortical layer of the femoral head

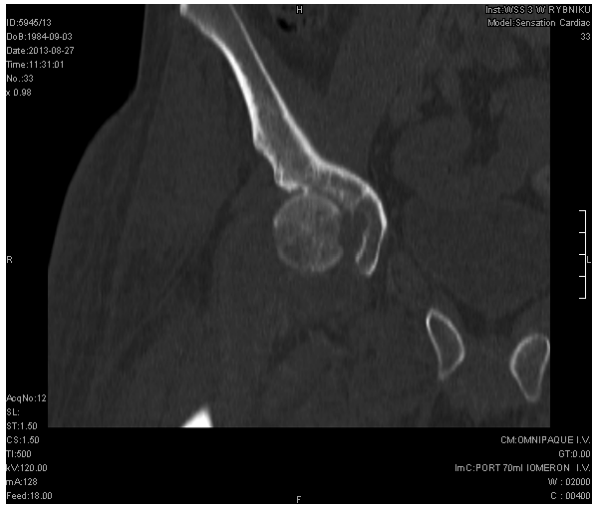

Figure 7. Computed tomography of the chest, abdomen, and pelvis; right hip joint. Around the head of the right femur, pathological structures with densities up to 30 UH (liquid-fluid) visible between the tense capsule and the outlines of the cortical bone layer

According to the Gaechter and Stutz classification of joint inflammations, stage IV arthritis was diagnosed with infiltration and undermining of cartilage as well as radiological signs of subchondral osteolysis and erosions [7, 8] (Fig. 6, 7). According to the algorithm for the management of infectious arthritis in the case of cartilage destruction, the joint should be resected and a limp joint should be formed [7–9]. The patient was transferred to the Orthopaedic Department, where the capsule, head, and femoral neck were removed (Girdlestone procedure). *Staphylococcus aureus* was isolated by a pus culture. In the postoperative period, the patient was respiratorily insufficient with symptoms of septic shock. The patient was transferred again to the ICU, where artificial ventilation, continuous haemofiltration, intensive antibiotic therapy, and circulatory support were used. After normalisation of inflammatory parameters and creatinine concentration and improvement of his general condition the patient was transferred to the Department of Oncology, where the ABVD chemotherapy was continued. In the CT scan after the fourth ABVD cycle, a reduction in lesions meeting stable disease (SD) criteria according to RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 was described. A continuation of the treatment was ordered; however, due to the suspicion of knee arthritis during the next stay, the therapy was completed at this stage. The knee joint puncture did not confirm the bacterial aetiology. The patient underwent partial oral sanation with the extraction of affected teeth. In a PET CT examination performed after eight administration of ABVD chemotherapy (four full cycles) and two CHOP administrations, no active disease features were described. The patient was referred to the Department of Radiotherapy. An important element of further therapy was rehabilitation, to improve the functionality of patients with so-called hanging hip and provide him with the highest level of independence. Subsequently, the patient did not report for scheduled follow-up visits. Based on the hospital records, the patient was determined to die in 2017 due to alcoholic liver failure and bleeding from oesophageal varices.

Discussion

According to the current guidelines, patients with advanced HL with clinical stage IIB and the presence of poor prognosis factors should receive 6–8 cycles of ABVD chemotherapy followed by IF-RT at 20–36 Gy for residual or primary tumour [6]. However, due to the delay of proper diagnosis and purulent lesions causing numerous and dangerous complications during the treatment the management in the presented case was significantly impeded. Delaying the proper diagnosis may not only reduce the chances of the patient being cured, but also pose an immediate threat to life, as in the case described, due to acute respiratory failure.

The time period from the collection of material for histopathological verification and immunohistochemical studies was two months. The purulent lesions with a staphylococcal aetiology occurring in the patient complicated and confused the picture of the underlying disease. After surgical treatment and targeted antibiotic therapy, they retreated and appeared in a different location. There are available in medical literature the case

reports of HL symptoms, especially the nodular sclerosis form with abscesses of various locations: abscess in the chest wall, liver, lung, spleen, axillary region, or pancreas [10–15]. The cultures of such abscesses were mostly aseptic, which indicated their non-infectious aetiology and should suggest the widening of the diagnosis. Such an unusual manifestation of the disease made diagnosis difficult, also due to the problem of obtaining material for histopathological examination; this contributed to therapeutic failures [15].

In the presented case, purulent lesions were associated with staphylococcal infection. The co-incidence of HL and *Staphylococcus aureus* infections are rare. Immunity disorders typical for HL are associated with decreased capacity of lymphoid dendritic cells (plasmacytoid dendritic cells — s-pDCs) to produce interferon-α (IFN-α) and a reduced number of circulating CD4 + T cells [16]. These disorders mainly cause weakness of cellular immunity and contribute to systemic, opportunistic viral, fungal, protozoan, or tuberculous infections [16–22]. The spectrum of infections occurring in patients with HL is similar to other immune disorders such as acquired immunodeficiency syndrome (AIDS), glucocorticoid therapy, severe combined immunodeficiency syndrome (SCID), or Di George syndrome [16]. In the case of bacterial infections in HL, causing serious infections confirmed in a microbiological study, *Streptococcus pneumoniae* is a common aetiological factor [19]. Coexistence of *Staphylococcus aureus* infection and HL is extremely rare [23]. The only description of wrist bone osteomyelitis of staphylococcal aetiology in a patient with HL is available in the literature [23]. Bone infections with other aetiologies are also described. In presented cases of bone and marrow infections (osteomyelitis), the infection was caused by bloodstream, usually due to a wound or soft tissue damage [22–24].

According to a study by Raluca-Ana Rus, published in the "Journal of Research in Medical Sciences" in 2018, concerning infections associated with chemotherapy in patients treated for haematological malignancies, in 34.4% of HL patients infectious complications were observed, among them 21.9% were bacterial infections, 9.4% — fungal, 3.1% — viral, while in the remaining 6.3% no aetiology was established [25]. The most common bacterial infection in patients with HL observed during chemotherapy was *Clostridium difficile* infection [25].

Purulent, blood-borne hip infection in adults is very rare [8, 10, 11, 26–28]. The correct diagnosis is extremely important because of the serious consequences of the disease [26–30]. According to the literature, the risk of *Staphylococcus aureus* infection increases in cases of tissues disruption, the presence of a foreign body in tissues, or comorbidities, such as: cancer, metabolic diseases, and immunosuppressive or anticancer therapy [24, 26, 27]. The main risk factors of staphylococcal bone infections are coexistent tissue blood supply disorders (e.g. in course of diabetes or vascular disease), high clinical stage of the cancer (e.g. HL with the presence of bone lesions — stage IV), and bone growth period when the bone is more susceptible to infection — hence osteoarthritis is more common in children. Anticancer treatment, such as chemo- and radiotherapy, is an additional risk factor [24, 25, 29, 30]. In the presented case, bone inflammation was probably blood-borne and was a consequence of changes either in the skin and soft tissues or teeth and could be associated with the chemotherapy used, as well as the presence of a malignant tumour and its advanced clinical stage.

References

1. Eichenauer DA, Engert A, Dreyling M, et al. ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011; 22 Suppl 6: vi55–vi58, doi: 10.1093/annonc/mdr378, indexed in Pubmed: 21908505.
2. Wróbel T. Chłoniak Hodgkina. In: Krzakowski M, Warzocha K (eds). Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych 2013 r. Via Medica, Gdańsk 2013, 981–990.
3. Wojciechowska U, Didkowska J. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie. http://onkologia.org.pl/chloniak-hodgkina-c81/.
4. Meder J. Chłoniak Hodgkina. In: Krzakowski M, Jędrzejczak WW, Kowalczyk JR. et al. (eds). Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych 2011 r. Via Medica, Gdańsk 2012: 704–716.
5. Hasenclever D, Diehl V, Armitage J, et al. A Prognostic Score for Advanced Hodgkin's Disease. New England Journal of Medicine. 1998; 339(21): 1506–1514, doi: 10.1056/nejm199811193392104.
6. National Comprehensive Cancer Network. Hodgkin lymphoma (verson 2.2014). hpttp://www.nccn.org/professionals/physicians_gls/pdf/hodgkins.pdf.
7. Górecki A, Marczyński W, Babiak I. Zasady profilaktyki, rozpoznawania i leczenia nieswoistych zakażeń kości i stawów. Ortop Traumatol Rehabilit. 2008; 4(6); 10: 396415.
8. Babiak I, Kowalewski M, Szczęsny G, et al. Zapalenia kości i stawów — charakterystyka u dzieci i dorosłych. Zakażenia. 2004; 6.
9. Vukasinović Z, Spasovski D, Cobeljić G, et al. Septic arthritis of the hip in infancy — diagnostic and therapeutic possibilities. Srp Arh Celok Lek. 2006; 134(1–2): 77–81, indexed in Pubmed: 16850583.
10. Karimi S, Mohammadi F, Pejhan S, et al. An unusual presentation of Hodkin's lymphoma as a chest wall abscess in association with old tuberculosis. Tanafoss. 2007; 6: 71–74.
11. Zaman A, Bramley PN, Wyatt J, et al. Hodgkin's disease presenting as liver abscesses. Gut. 1991; 32(8): 959–962, indexed in Pubmed: 1885082.
12. Pickerill RG, Kaplan PD, Shively JG, et al. Hodgkin's lymphoma presenting as lung abscess. Pa Med. 1987; 90(11): 64–65, indexed in Pubmed: 3696728.
13. Bloom RA, Freund U, Perkes EH, et al. Acute Hodgkin disease masquerading as splenic abscess. J Surg Oncol. 1981; 17(3): 279–282, indexed in Pubmed: 7253662.
14. Telfah MM. Hodgkin's lymphoma presents as an inguinal abscess: a case report and literature review. BMJ Case Rep. 2012; 2012, doi: 10.1136/bcr-2012-006219, indexed in Pubmed: 23001092.
15. Pawłowski W, Dorobisz T. Katastrofa terapeutyczna jako następstwo trudności diagnostycznych u 52-letniego pacjenta leczonego z powodu ropnia trzustki. Pol Merkur Lekarski, 2015; XXXIX; 232: 231–233.
16. Shodell M, Kempin S, Siegal FP. Plasmacytoid dendritic cell and CD4 + T cell deficiencies in untreated Hodgkin disease: implications for susceptibility to opportunistic infections. Leuk Lymphoma. 2014; 55(11): 2656–2657, doi: 10.3109/10428194.2014.893312, indexed in Pubmed: 24547707.
17. Simpson JF. Listeria monocytogenes meningitis: an opportunistic infection. J Neurol Neurosurg Psychiatry. 1971; 34(6): 657–663, indexed in Pubmed: 4110448.

18. Diddie KR, Schanzlin DJ, Mausolf FA, et al. Necrotizing retinitis caused by opportunistic virus infection in a patient with Hodgkin's disease. Am J Ophthalmol. 1979; 88(4): 668–673, indexed in Pubmed: 228556.
19. Notter DT, Grossman PL, Rosenberg SA, et al. Infections in patients with Hodgkin's disease: a clinical study of 300 consecutive adult patients. Rev Infect Dis. 1980; 2(5): 761–800, indexed in Pubmed: 6763305.
20. Newton R, Crouch S, Ansell P, et al. Hodgkin's lymphoma and infection: findings from a UK case-control study. Br J Cancer. 2007; 97(9): 1310–1314, doi: 10.1038/sj.bjc.6603999, indexed in Pubmed: 17895891.
21. de Armas Y, Capó V, González I, et al. Concomitant Mycobacterium avium infection and Hodgkin's disease in a lymph node from an HIV-negative child. Pathol Oncol Res. 2011; 17(1): 139–140, doi: 10.1007/s12253-010-9275-5, indexed in Pubmed: 20467849.
22. Kumar R, Daga MK, Kamble NL, et al. Rare association of Visceral leishmaniasis with Hodgkin's disease: A case report. Infect Agent Cancer. 2011; 6(1): 17, doi: 10.1186/1750-9378-6-17, indexed in Pubmed: 22011565.
23. Hayes TG, Gill EP, Swarna U. Osteomyelitis of the wrist in a patient with Hodgkin's disease. J Intern Med. 1991; 229(5): 467–469, indexed in Pubmed: 2040874.
24. Wald ER. Risk factors for osteomyelitis. Am J Med. 1985; 78(6B): 206–212, indexed in Pubmed: 3893117.
25. Rusu RA, Sîrbu D, Curşeu D, et al. Chemotherapy-related infectious complications in patients with Hematologic malignancies. J Res Med Sci. 2018; 23: 68, doi: 10.4103/jrms.JRMS_960_17, indexed in Pubmed: 30181750.
26. Razak M, Nasiruddin J. An epidemiological study of septic arthritis in Kuala Lumpur Hospital. Med J Malaysia. 1998; 53 Suppl A: 86–94, indexed in Pubmed: 10968188.
27. De Souza HM, Helito CP, Oliva GB, et al. Clinical and epidemiological characteristics of septic arthritis of the hip, 2006 to 2012, a seven-year review. Clinics (Sao Paulo). 2014; 69(7): 464–468, indexed in Pubmed: 25029577.
28. Cierny G, Mader JT. Approach to adult osteomyelitis. Orthop Rev. 1987; 16(4): 259–270, indexed in Pubmed: 3454938.
29. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med. 1970; 282(4): 198–206, doi: 10.1056/NEJM197001222820406, indexed in Pubmed: 4902833.
30. Karlinj M. Osteornyelitis in children. Cliri Pedintr Med Surg. 1987; 4: 37–56.