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Professor Krzysztof Krzemieniecki Award for the best case report accepted for publication

Case Report Contest Policies

This policy defines the scope, requirements and regulations regarding **The Krzysztof Krzemieniecki Award** for the best case report published in "Oncology in Clinical Practice" (OCP) Seventh Edition.

1. The aim of the contest is to encourage submission of quality case reports related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1, 2022 and May 31, 2023 and accepted for publication will qualify.
3. Manuscripts should be prepared in line with Authors' guidelines and should be submitted only through the manuscript system available at Journal's website: https://journals.viamedica.pl/oncology_in_clinical_practice
4. All submitted manuscripts will be evaluated during the peer review process and authors will be informed about their qualification for publication in OCP. Accepted papers will be evaluated by the Contest Committee based upon fulfillment of the Contest criteria as well as practical significance, originality, applicability and addressing of current/critical concerns.
5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
6. Results will be announced during the XXVI National Congress of The Polish Society of Clinical Oncology and subsequently at the Journal website.
7. Winner will be notified via email.
8. Contest Committee may exclude a paper from participation in case of potential conflict of interest or ask submitting author for adequate clarifications.
9. The Sponsor at any stage and in any respect, will not participate in the evaluation of entries and selection of a winning paper.
10. The award amount shall be paid based on the copyright transfer agreement to the paper.
11. These Regulations are the sole and exclusive document defining the principles and conditions for the Contest. In all matters not regulated, decisions are made by The Organizer.

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Recommendations for prevention of SARS-CoV-2 infection in immunocompromised patients

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Introduction

The appearance of the new SARS-CoV-2 coronavirus at the end of 2019 changed the reality and created a serious health threat on a global scale. The COVID-19 pandemic has killed more than 6 million people, and officially registered infections amount to 600 million. In Poland, 117 000 people have died, and the number of registered infections has exceeded 6 million; however, these numbers certainly do not reflect the actual values. In the last 2 years, risk factors for severe COVID-19 have been identified. In addition to cardiovascular diseases and metabolic diseases (diabetes, obesity), they include conditions associated with impaired immune system functions, either due to the disease process itself or as a result of treatment. These factors have double significance at present. In addition to the risk of a severe course of the disease, they also bring the risk of an inadequate response to COVID-19 vaccination, often implying the lack of any specific immunity.

In this article, we present the position of experts in oncology, hematology, transplantation (representing the Polish Oncological Society, the Polish Society of Hematologists and Transfusionists, and the Polish Society of Transplantation), and infectious diseases on COVID-19 prevention in the immunocompetent population. This population includes patients with solid tumors, hematological malignancies, and patients after hematopoietic cell/solid organs transplantation. To find relevant scientific evidence, a non-systematic search of clinical practice guidelines and medical information databases was performed. The legitimacy of using all currently available forms of prophylaxis does not raise any doubts, and numerous clinical observations, including Polish ones, confirm the importance of proper management, especially in this group of patients. The availability of vaccines against COVID-19 and the evolution of the virus (the emergence of new subtypes of the Omicron variant) gives hope for a gradual reduction in mortality. However, the discussed group of patients is still at risk of a severe course of disease due to the ineffectiveness of commonly accepted management strategies. Moreover, any delays in the treatment of underlying diseases resulting from SARS-CoV-2 infection carry a risk of poor prognosis.

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The course of SARS-CoV-2 infection in patients with solid organs malignancies (SOMs)

Effect of tumor type

Solid tumors *per se* have a smaller adverse effect on the course of SARS-CoV-2 infection compared to hematological malignancies; however, a worse ECOG performance status (PS) and a higher cancer stage in patients with solid tumors are associated with a higher risk of death due to COVID-19 [1]. The risk of having to be admitted to the intensive care unit (ICU) and the risk of death in this group increase by about 50–66%. Of course, this may be partly due to the specific age structure of cancer patients (older compared to the general population). Regardless of this, however, it is believed that diagnosis of SOMs is an independent risk factor for death and hospitalization in ICU due to SARS-CoV-2 infection.

The coexistence of COVID-19 with bilateral lung involvement and simultaneous lung cancer, both primary lung cancer and metastatic lesion, is a particularly life-threatening combination, increasing the risk of death [2]. This was also confirmed by the Polish report under the National Oncological Strategy "Impact of the COVID-19 pandemic on the cancer care system". The 30-day mortality rate among patients with lung and thoracic cancers exceeded 23%, with an expected mortality of 10.9% [standardized mortality ratio (SMR) = 2.27]. The worse course of COVID-19 may also be associated with tobacco-dependent neoplasms [3]. Moreover, the negative consequences of previous COVID-19 infection affect approximately 15% of cancer patients and have a negative impact on oncological treatment outcomes due to the need to interrupt/delay cancer therapy [4].

Effect of anticancer treatment type

Active systemic treatment of patients with solid tumors, especially cytotoxic chemotherapy, is associated with the risk of a more severe course of SARS-CoV-2 infection and an increased risk of hospitalization and death [1, 5–7]. The results of the meta-analysis did not show such a relationship in the case of molecularly targeted therapy, immunotherapy, or radiotherapy. In turn, many studies, including meta-analyses, have confirmed the negative impact of active SARS-CoV-2 infection during the postoperative period in cancer patients treated with surgery [8, 9].

The course of SARS-CoV-2 infection in patients with hematological malignancies

Effect of malignancy type

Analyzes of the correlation between malignancy type and the course of COVID-19 demonstrated conflicting results, but in most studies, acute myeloid leukemia (AML) was associated with a higher risk of death, exceeding even 40% [10]. In other analyzes, higher mortality was observed in patients with non-Hodgkin lymphomas (NHL), plasma cell neoplasms [11], or myelodysplastic syndrome (MDS) [12]. In a multicenter retrospective study, a severe course of COVID-19 (defined as hospitalization with the need for oxygen therapy or ICU admission) was observed in 65.6% of patients with chronic lymphocytic leukemia (CLL). The mortality rate was 27.3% (38.4% in patients with severe COVID-19) [13]. In the Polish analysis of 192 patients with CLL, the mortality rate was also high, amounting to 30% [14]. Relatively consistent data concern the milder course of COVID-19 in patients with chronic hematological malignancies, with the mortality rate in patients with chronic myeloid leukemia (CML) of 5.5% compared to 2.97% in the general population [15, 16]. Similarly, the diagnosis of a Ph-negative myeloproliferative neoplasm is associated with lower mortality compared to other neoplasms [17].

Effect of anticancer treatment type

Studies on the impact of specific anticancer treatments on the COVID-19 course did not report unequivocal results. In a meta-analysis of 34 studies, the type of treatment used was not associated with the severity of COVID-19 course or increased risk of death [18]. Smaller studies have shown that treatment with monoclonal antibodies, especially anti-CD20, was associated with higher mortality, longer hospitalization time, and a higher risk of death [17].

The use of chemotherapy is generally not associated with a worse prognosis [19] although one study reported a four-fold higher risk of death in patients undergoing intensive treatment, for example, high-dose methotrexate, DHAP (cisplatin, cytarabine, dexamethasone), escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), intensive chemotherapy in the treatment of patients with acute leukemia, as well as autologous and allogeneic hematopoietic stem cell transplantation (auto-, alloHSCT) [20, 21]. In a multi-center prospective analysis, the mortality rate due to COVID-19 in patients after HSCT was 28.4%, with no difference in survival between patients after alloSCT and autoSCT [22]. Chimeric antigen receptor-T cell (CAR-T) immunotherapy is associated with an even higher risk of death due to COVID-19, amounting to 41% [23].

Currently, no data suggest that drugs used in the treatment of patients with chronic myeloproliferative neoplasms (MPN), such as tyrosine kinase inhibitors, hydroxyurea, interferon alpha, anagrelide, or ruxolitinib increase the risk of SARS-CoV-2 infection or a severe course of the disease.

The course of SARS-CoV-2 infection in patients after transplantation

Patients after organ transplantation are at increased risk of infection and severe course of SARS-CoV-2 infection not only due to the weakened immune response caused by immunosuppressive treatment but also due to frequent comorbidities, such as diabetes, hypertension, or ischemic heart disease. The course of COVID-19 in transplant recipients is associated with increased morbidity and mortality. Published data show that mortality in transplant recipients in the first year of the pandemic was about 20%, while in the second year (2021), it decreased to several percent due to the introduction of vaccinations and more effective drugs. However, mortality in transplant patients was still higher than in the general population [24, 25].

Both the humoral and cellular responses to SARS-CoV-2 infection are weaker and disappear faster than in immunocompetent individuals. Similarly, the response to vaccination is poorer and of short duration, hence the fourth dose of vaccine is currently recommended.

The optimal regimen of immunosuppression in SARS-CoV-2 infected transplant recipients has not been established, therefore, the reduction of immunosuppression is dependent on the clinical course. In mild and moderate cases, it is recommended to discontinue the antiproliferative drug (mycophenolate mofetil). In severe cases, it is recommended to temporarily discontinue immunosuppressants and administer intravenous glucocorticosteroids. After 14 days, immunosuppression should be slowly increased. In patients without infection, the immunosuppressive treatment should not be modified [26, 27].

Additional therapies for SARS-CoV-2 infection may be used in transplant recipients taking into account their side effects, drug-drug interactions, and renal function [28, 29]. The response to vaccination and treatment may change with the emergence of new viral mutations [30, 31].

Effectiveness of vaccinations against COVID-19 in cancer patients

Patients with solid organs malignancies

Vaccination against COVID-19 is the basic method of reducing the risk of infection and the severe course of COVID-19 also in the group of patients with solid tumors [32]. The safety profile of vaccines based on mRNA technology is very good in this group of patients [33]. International guidelines currently recommend mRNA vaccines in cancer patients, with supplementary and booster doses [34]. A complete course of vaccination significantly reduces the risk of death in these patients. Most patients develop antibodies to SARS-CoV-2 [34, 35], but the production of antibodies (serological response) occurs after a longer period or at a lower titer than in the general population [36, 37]. This is particularly evident during active chemotherapy [38, 39]. In cancer patients, antibodies titer and the level of cellular response indicators decrease faster, which translates into lower protective effectiveness of vaccinations. In addition, the current dominance of the Omicron variant reduces the effectiveness of vaccination due to the antigenic differences between the vaccine and the current virus variant [40].

Patients with hematological malignancies

The same immunodeficiency mechanisms accompanying proliferative neoplasms of the lymphatic and hematopoietic systems that are associated with an unfavorable course of infection, including COVID-19, also contribute to a suboptimal response to vaccination against COVID-19. Compared to healthy subjects, lower antibody titers, shorter persistence of the post-vaccination response, and impaired antibody function are observed [41]. A large part of published data is based on the analysis of post-vaccination antibody production, ignoring cell-mediated immunity, which limits the full clinical conclusion on vaccine efficacy.

A Polish analysis [42] compared the effectiveness of vaccinations in the groups of two immune system cancers with significant immunodeficiency: multiple myeloma (MM) and CLL. A statistically significant increase in antibody titers was observed in patients with MM after the second dose of the primary vaccination, significantly greater than in patients with CLL. The antibody response rate in the CLL cohort was 41% after the second dose and increased to 71% at 12 weeks after the second dose of the vaccine. The rate of seroconversion in the CLL cohort did not correlate with age, disease stage, or sex. The results of recent studies have also shown significantly lower antibody titers in patients receiving anti-cancer therapy, especially those undergoing CAR-T and bone marrow transplant procedures. In patients with MM treated with targeted anti-CD38 or BCMA (B-cell maturation antigen) therapy and patients with lymphomas and CLL treated with anti-CD20 immunochemotherapy or Bruton tyrosine kinase (BTK) inhibitors, a poorer vaccine response has been observed. Stampfer et al. [43] reported lower antibody titers in patients receiving steroids, but this was not observed in Polish patients.

Vaccines against COVD-19 are effective in inducing the production of antibodies and increasing the titer of anti-RBD (receptor-binding domain) antibodies, which persist for at least 3 months after the second dose. Vaccination effectiveness is increased by 30% by a booster dose, and the persistence of antibodies is prolonged.

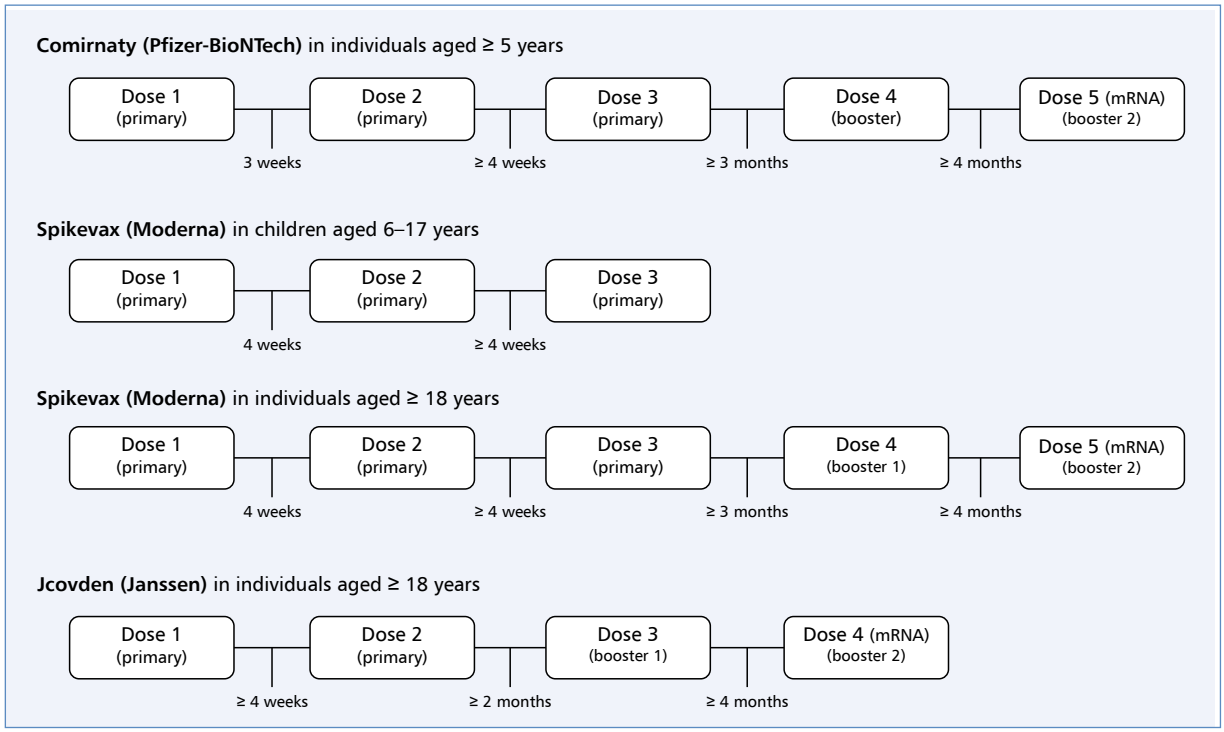

Figure 1. Recommendations for the time of administration of subsequent doses of vaccines against COVID-19 in people with severe or moderate immunodeficiency (based on: mp.pl — szczepienia and https://www.cdc.gov/vaccines/covid-19/clinicalconsiderations/interim-considerations-us.html]

Patients after organ transplant

In dialysis patients, a slightly delayed but good response to vaccination was observed [44, 45]. Patients after kidney transplantation responded to vaccination much worse. Only about 50% of patients achieved seroconversion after a two-dose mRNA vaccination, and the antibody titer was frequently lower than in the general population [46, 47]. In addition to patients' older age, factors adversely influencing the humoral response included immunosuppressive treatment, in particular intensive one and with use of polyclonal antibodies in induction therapy, as well as the use of antiproliferative drugs from the mycophenolate group in maintenance therapy [48, 49]. Due to the above data on the response to vaccination with the two-dose vaccination regimen in the population of patients treated with renal replacement therapies, including patients after transplantation, it is recommended to administer three doses of primary vaccination and treat the third dose as supplementary to the primary vaccination course. A primary cycle of 3 doses and a fourth booster dose after 5–6 months is now recommended.

In patients after transplantation, the clinical effectiveness of vaccinations is worse, which results from impaired immune response to vaccination (54% after the second dose, 67% after the third dose) [50].

Recommendations for the use of COVID-19 vaccines in non-immunocompetent individuals with severe or moderate immunodeficiency

The World Health Organization (WHO) has already issued a recommendation for an extended series of primary immunizations (i.e. third dose) and booster doses (i.e. fourth dose) in immunocompromised individuals for all COVID-19 vaccines. It is allowed to use booster doses in the form of homologous (the same vaccine platform) and heterologous (different vaccine platform) vaccines [51, 52].

Figure 1 shows the recommended COVID-19 immunization schedule for people with severe to moderate immunodeficiency.

Individuals 12 years of age and older should receive a booster dose (fourth) at least 5 months after the supplementary dose (third).

If possible, doses of COVID-19 vaccine should be administered at least 2 weeks before starting or resuming immunosuppressive therapy. The timing of vaccination against COVID-19 should consider current or planned immunosuppressive therapy, as well as optimization of both the patient's clinical state and response to the vaccine.

Currently, it is not recommended to perform serology or cellular response tests to assess response to vaccination against COVID-19.

The same preparation (i.e. from the same manufacturer) should be used for the primary vaccination, including the administration of a supplementary dose. In exceptional circumstances, where it is not possible to determine which mRNA vaccine was administered as the first dose of the baseline regimen, or if this preparation is not available, any other available mRNA vaccine may be administered to complete an already initiated regimen, with an interval of at least 28 days between doses. In people aged 18 years and above, in exceptional situations, when the patient received the first dose of mRNA vaccine, but it is not possible to complete the schedule with the same preparation or another mRNA vaccine (e.g. due to contraindications), administration of 1 dose of Janssen/Johnson & Johnson (J/J&J) vaccine may be considered at least 28 days apart to complete the schedule. Patients who receive the J/J&J vaccine after a dose of mRNA vaccine to complete the schedule that has been initiated should be considered vaccinated with a 1-dose J/J&J preparation.

Any age-appropriate mRNA preparation may be used as a booster (following a heterologous pattern). Jcovden (J/J&J) should not be used for the second booster vaccination.

Vaccination against COVID-19 is recommended for all people, regardless of previous SARS-CoV-2 infection (symptomatic or asymptomatic), and this applies to both basic vaccination, including administration of the supplementary dose, and booster vaccination. This recommendation applies to people infected with SARS-CoV-2 before vaccination against COVID-19 or between subsequent vaccination doses.

Additional booster doses for immunocompromised people

Additional booster doses in addition to the first supplementary dose are currently offered in some countries (i.e. fourth dose for the elderly and fifth dose for immunocompromised people). Data on the effectiveness of these additional boosters are sparse and do not predict the duration of continued protection. Data on additional booster doses are available only for mRNA vaccines [53].

Recommendations for passive immunoprophylaxis in non-immunocompetent individuals

On March 25, 2022, the European Medicines Agency (EMA) registered the Evusheld® preparation containing a combination of two antibodies (tixagevimab and cilgavimab) with prolonged action, for COVID-19 pre-exposure prophylaxis [54]. The preparation can be used in adults and adolescents aged 12 years and older who weigh at least 40 kg. The prerequisite for eligibility is the lack of a current SARS-CoV-2 infection, defined as exposure to a person infected with SARS-CoV-2 and the presence of moderate or severe immunodeficiency. The latter parameter, in accordance with the data cited earlier, may cause an insufficient immune response to vaccination against COVID-19. In addition, the preparation is intended for people who cannot receive any available COVID-19 vaccine. Administration of Evusheld® should be considered especially in people who are at particular risk of severe course of COVID-19.

The drug is administered by intramuscular injection and exhibits neutralizing activity against the Omicron SARS-CoV-2 variant, which is unique among currently available monoclonal antibodies. The drug does not replace the COVID-19 vaccine and should not be used in people without contraindications to vaccination, who are expected to respond adequately to the vaccine. Patients who have been vaccinated against SARS-CoV-2 may receive Evusheld® 2 weeks after the last dose of the vaccine at the earliest. However, vaccination can be performed regardless of when Evusheld® was administered.

Current registered drug dosage in Europe is 150 mg tixagevimab and 150 mg cilgavimab administered as two consecutive intramuscular injections.

Evusheld® has been registered based on the results of the PROVENT clinical trial. In this phase III, randomized, double-blind, placebo-controlled trial, the use of tixagevimab/cilgavimab for pre-exposure prophylaxis in a group of 5197 subjects was investigated. There was a 77% reduction in the risk of symptomatic COVID-19 confirmed by a positive SARS-CoV-2 RT-PCR (real-time polymerase chain reaction) test in the TIXA/CILGA arm compared to placebo after 3 months and 83% after 6.5 months of follow-up [55].

Evusheld® is the optimal form of prophylaxis in non-immunocompetent patients whose response to vaccination is unsatisfactory, short-term, or absent. The protective effect of antibodies lasts for at least 6 months [56].

The use of other monoclonal antibodies, such as bamlanivimab/etesevimab or casirivimab/imdevimab for pre-exposure prophylaxis, is currently not justified due to the dominance of the Omicron SARS-CoV-2 variant, which is not neutralized by these antibodies.

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Common statement of experts of the Polish Oncological Society, Polish Lung Cancer Group, Polish Society of Lung Diseases, Polish Society of Gastroenterology, Polish Society of Endocrinology, and the Polish Society of Cardiology for minimal requirements in diagnosis and monitoring of selected adverse events of immunotherapy in oncological patients

Introduction

The introduction of a new treatment strategy — immunotherapy — based on fighting the neoplasm by activation of the immune system, has contributed to a considerable prolongation of overall survival of cancer patients [1–4]. The drugs which activate the immune system are generally immune checkpoint inhibitors (ICIs,), which include monoclonal anti-CTLA-4 (anti-cytotoxic T lymphocyte antigen-4) and anti-PD-1/L1 (anti-programmed cell death 1/ligand 1) antibodies. Currently, the following ICIs have been registered by the American Food and Drug Administration (FDA) and/or the European Medicines Agency

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(EMEA): anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab, pembrolizumab, cemiplimab), and anty-PD-L1 (atezolizumab, avelumab, durvalumab) [4].

There is a problem with the occurrence of specific toxicities associated with the use of immunotherapy — the so-called immune-related adverse events (irAE), which in some cases can be very serious or even lead to death. It should also be pointed out that currently ICIs are more and more frequently used together with other drugs, for example, chemotherapy (lung cancer), targeted therapy (kidney cancer) or as combination therapy (melanoma, lung cancer) [5], which may increase the risk of occurrence and intensification of adverse effects. Therefore appropriate qualification of patients for immunotherapy and appropriate monitoring are of paramount importance. Continuous education of medical personnel and patients and their family (caregivers) is also indicated.

This article presents the joint statement of scientific associations (Polish Oncological Society, Polish Lung Cancer Group, Polish Society of Lung Diseases, Polish Society of Gastroenterology, Polish Society of Endocrinology, and the Polish Society of Cardiology) defining the minimal diagnostic requirements (laboratory and imaging parameters) in diagnosing, monitoring, and treatment of the most common adverse events of immunotherapy in patients with malignant neoplasms.

Recommended procedure before and during immunotherapy with ICIs

A detailed medical history and appropriate additional tests before and during immunotherapy are the most important for patient safety during treatment with immune checkpoint inhibitors. It should be noted that irAEs can affect practically any organ and occur at various stages of treatment (frequently even after immunotherapy is completed) [6–11]. The mechanisms through which immunotherapy exerts its antineoplastic activity are also responsible for irAE development. These are, namely, activated T lymphocytes escaping from central control because of the inhibition of immune checkpoints, which unfortunately may lead to uncontrolled irAE development. It is particularly important to note that initially mild symptoms may in a short time intensify considerably and lead to a severe course of irAEs. Therefore, it is extremely important to perform appropriate analyses before immunotherapy and to monitor patients during treatment. The recommended procedure and analyses before and during immunotherapy are presented in Table 1.

The next aspect is the need for continuous education of patients and their family (caregivers) about the possibility of occurrence and the course of irAEs. A good clinical practice should be providing patients with appropriate materials with information (e.g. informative brochures, reference charts) about irAEs and about procedures in the case of their appearance. Patients should also be informed about using appropriate contraception when ICIs are administered, and the problems of procreation should always be discussed before initiating treatment.

There are few data on the use of ICIs in patients with pre-existing autoimmune diseases, because in most cases they were excluded from clinical trials due to concerns that autoimmune diseases may increase the risk of severe irAEs. However, an analysis of the literature data on the use of ICI in patients with pre-existing disease indicates no increase in the incidence of new irAEs, but unfortunately exacerbation of pre-existing autoimmune disease [12]. Due to the high probability of autoimmune disease exacerbation, clinical decisions regarding the use of ICI in patients with ongoing autoimmune disease should be carefully analyzed and the benefits of ICI therapy should outweigh the possible consequences of autoimmune disease exacerbation.

Immne releted adverse events associated with the gastrointestinal tract

Gastrointestinal irAEs are most common during treatment with immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PD-L1) and in some cases can be severe and even fatal. Therefore before startingimmunotherapy, a medical historyshould be collected about diseases of the gastrointestinal tract and also the motor activity of the alimentary canal (frequency of defecation, consistency of stool), to determine if after initiation of treatment an actual change has occurred and the number of defecations has increased [13–19].

It is extremely important to collect information concerning the following diseases:
— ulcerative colitis
— Leśniowski-Crohn disease,
— autoimmune hepatitis,
— microscopic colitis,
— chronic diarrhea (functional).

In the case of coexistence of ulcerative colitis, Leśniowski-Crohn disease, or autoimmune colitis, the risk of exacerbation of these diseases during immunotherapy should be taken into consideration, as well as the increased risk of irAEs.

Table 1. Recommended procedures and examinations before and during immunotherapy

Examinations before immunotherapy	Frequency of examinations during immunotherapy
Anamnesis for diseases: • autoimmunological (ulcerative colitis, Leśniowski-Crohn's disease, connective tissue diseases, etc.) • endocrinological (thyroid, pancreas diseases, etc.) • other organs (cardiac and vascular diseases, kidney failure, hematological diseases, etc.)	Evaluation of potential adverse effects during each visit and before each immunotherapy administration
Anamnesis for infectious diseases: • as required analyses — HBsAg, HBsAb, HBcAb, hCAb, CMV antibodies, T-spot test, HIV antibodies, HIV antigen (p24)	Tests are important if patients develop irAEs and immunosuppressive treatment is required such as glucocorticosteroids and/or anti-TNFa treatment
Initial evaluation of gastrointestinal tract function: • defecation frequency, stool consistency	Evaluation during each visit and before ICIs administration
Examination of skin: • examination of skin and mucous membranes with evaluation of the extent and type of occurring lesions	Evaluation during each visit and before ICIs administration
Imaging studies: • evaluation of disease stage (CT, MRI, PET-CT) depending on the indications • central nervous system MRI depending on the indications	Periodic imaging studies depending on drug program and indications
Laboratory analyses: • CBC with differential • ALAT, ASPAT, ALP • Bilirubin • Creatinine • Urea • Electrolytes (Na, K, Ca) • Glucose • Total protein • Albumins	Tests every 4–6 weeks during immunotherapy (or before each dose of immunotherapy), depending on the drug program and indications
Thyroid: • TSH • fT4	Tests every 4–6 weeks during immunotherapy (or before each dose of immunotherapy), depending on the drug program and indications
Cardiovascular system: • ECG • Consider laboratory tests for cardiac troponin and NT-proBNP • Cardiological consultation considered individually for patients with increased cardiovascular risk	Consider periodic tests in patients with irregular results or reporting symptoms
Respiratory system: • O_2 saturation level	Consider periodic tests in patients with irregular initial results
Musculoskeletal system: • examination/functional evaluation in patients with preexisting disease	Routine controls not required in asymptomatic patients
Pancreas: • preliminary tests not required	Routine controls not required in asymptomatic patients

ALAT — alanine aminotransferase; ALP — alkaline phosphatase; ASPAT — aspartate aminotransferase; CBC — complete blood count; CMV — cytomegalovirus; CT — computed tomography; fT4 — free thyroxine); HIV — human immunodeficiency virus; irAEs — immune-related adverse events; MRI — magnetic resonance imaging; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PET-CT — positron emission tomography-computed tomography; TNF — tumor necrosis factor alpha; TSH — thyroid stimulating hormone

Diarrhea and colitis

Diarrhea can be an indication of developing colitis or other serious and potentially life-threatening immunological toxicities. Diarrhea requires strict monitoring as it can lead in a very short time to significant dehydration, and as a consequence of water and electrolyteimbalance, to acute renal failure and death.

Diarrhea is among the most frequent immunological toxicities as well as one of the main symptoms of developing immune-mediated colitis. The remaining symptoms indicating colitis are predominantly abdominal pain and the presence of blood in the stool, weight loss, fever, nausea, and/or vomiting. Immune-mediated colitis may lead to many complications, including bowel perforation, anemia, necrosis, bleeding, and *megacolon toxicum*.

The following should be excluded in a differential diagnosis of diarrhea and toxicity:

— infection by Clostridium difficile or other pathogens [in each patient in whom intense diarrhea occurs during treatment with anti-CTLA-4, anti-PD-1, or anti-PD-L1, microbiological/mycological analysis of the stool should be performed as well as checking for infection by cytomegalovirus (CMV); immunoglobulin M (IgM); polymerase chain reaction (PCR)];
— occurrence of metastases to the digestive tract, especially in melanoma patients.

The examination of choice confirming the diagnosis of immunological colitis is colonoscopy with collection of samples for histopathology. The diagnosis of immunological colitis (without diarrhea) is generally based on histopathological analysis.

The differential diagnosis of grade 1 diarrhea or colitis should include complete blood count (CBC) with differential, hepatic and renal tests, electrolytes, and glucose. Additional analyses should be performed in patients with diarrhea and symptoms of colitis if they are ≥ G2 [20] and should comprise stool analysis (*C. difficile*), evaluation of calprotectin in the stool, or other examinations aimed at determining infection, including COVID-19 depending on the clinical indications. Determining thyroid stimulating hormone (TSH) and diagnosis of celiac disease (antibodies against transglutaminase together with total IgA concentration) is recommended if there is a clinical suspicion of celiac disease due to ICIs [13–19]. Disease progression or neoplasm dissemination in the abdominal cavity should also be excluded (in melanoma patients, metastases to the alimentary tract are common).

In cases of pronounced diarrhea or symptoms of colitis of grade ≥ 3 (G3/G4) or their long-term (≥ 5 days) persistence at grade 2 (G2), as well as in the case of doubts about the diagnosis of immunological toxicity, endoscopic analysis of the colon should be performed (sigmoidoscopy and/or colonoscopy), with taking sections for histopathological analysis [13–19]. In cases in which colonoscopy is ruled out, for instance, with suspicion of colon perforation or megacolon toxicum, computed tomography (CT), which is an effective and non-invasive option, should be performed. Irregularities in the CT picture associated with immunotherapy-induced colitis include mesenteric swelling and thickening of the colon wall.

Recommended additional analyses in patients with suspected/diagnosed diarrhea and/or immun-mediated colitis are presented in Table 2.

Table 2. Indicated additional tests in patients with suspected/diagnosed diarrhea and/or immune colitis

Laboratory analyses
CBC with differential
Creatinine, urea
Electrolytes (sodium, potassium, calcium)
ASPAT, ALAT
Bilirubin
Glucose
TSH, fT4
Test for CMV (IgM, PCR)
Imaging examinations
Abdominal USG
Computed tomography of abdominal and pelvis
Stool analysis
Bacteriological test (*C. difficile*)
Mycological test
Calprotectin in stool
Endoscopic examinations
Sigmoidoscopy with samples for histopathology
Colonoscopy with samples for histopathology

ALAT — alanine aminotransferase; ASPAT — aspartate aminotransferase; CBC — complete blood count; fT4 — free thyroxine; CMV — cytomegalovirus; IgM — immunoglobulin M; PCR — polymerase chain reaction; TSH — thyroid stimulating hormone; USG — ultrasonography

Hepatitis

Hepatitis associated with immune checkpoint therapy is generally asymptomatic and diagnosed by elevated serum alanine aminotransferase (ALT) and/or aspartate transaminase (AST). It should be noted that elevated levels of ALT/AST may also be associated with muscle damage, including the cardiac muscle; therefore, an extension of the diagnosis in this direction is recommended (creatine kinase levels, troponin, ECG, etc.).

In a differential diagnosis, the following factors should also be taken into consideration: the appearance or progression of metastases to the liver, cholestatic jaundice, infections [including hepatitis type B or C virus, CMV, Epstein-Barr virus (EBV), sepsis], hepatic vein thrombosis, diet (including alcohol consumption), use of

other drugs, stimulants, or supplements (alternative medicine) by the patient, other autoimmunological diseases, and genetic background or coexisting diseases. Laboratory analyses evaluating hepatic function should be performed before each immunotherapy infusion.

Diagnostic analyses at the moment of the occurrence of grade ≥ 2 toxicity should include ALT, AST, alkaline phosphatase, clotting estimation — prothrombin time/international normalized ratio (INR), bilirubin levels in serum, iron levels, autoimmunological panel for hepatitis: anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), anti-mitochondrial antibodies (AMA), peripheral ANCA (p-ANCA), anti-smooth muscle antibodies (ASMA), and analyses for hepatitis C virus (HCV), hepatitis B virus (HBV), and CMV, EBV [13–19].

In the case of hepatic toxicity of grade ≥ 3, abdominal imaging tests should be considered [e.g. computed tomography, magnetic resonance imaging (MRI), etc.] if the patient had prior liver disease or there is a suspicion of progression of the disease/metastasis to the liver.

A biopsy may be considered to determine the cause of unsuccessful therapy with steroids or suspicion of steroid-resistant immunological hepatitis [13–19].

Laboratory analyses [ALT, ASP, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), bilirubin, albumins, PT/INR] should be repeated once a week in the case of G1–G2 liver toxicity and every 1–2 days at toxicity ≥ G3.

Indicated additional examinations in patients with suspected/diagnosed autoimmune hepatitis are presented in Table 3.

Table 3. Indicated additional tests in patients with suspected/diagnosed immune hepatitis

Laboratory analyses
CBC with differential
Creatinine, urea
Electrolytes (sodium, potassium, calcium)
ASPAT, ALAT, ALP, GGTP
Bilirubin Glucose
Clotting system (PT/INR)
Albumins
TSH, fT4
Test for CMV (IgM, PCR), EBV
Test for HBV (HBsAg) and HCV (anti-HCV)
Panel for autoimmune hepatitis (ANA, ANCA, ASMA) — in selected cases
Imaging examinations
USG of the abdominal cavity
Liver MRI
Computed tomography of abdominal cavity and pelvis
Histopathological examinations
Liver biopsy (if no reaction to glucocorticoid treatment)

ALP — alkaline phosphatase; ALAT — alanine aminotransferase; ANA — anti-nuclear antibodies; ANCA — anti-neutrophil cytoplasmic antibodies; ASMA — anti-smooth muscle antibodies; ASPAT — aspartate aminotransferase; CBC — complete blood count; CMV — cytomegalovirus; EBV — Epstein-Barr virus; GGTP — gamma glutamyl transpeptidase; fT4 — free thyroxine; IgM — immunoglobin M; INR — international normalized ratio; HBV — hepatitis B virus; HCV — hepatitis C virus; MRI — magnetic resonance imaging; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PCR — polymerase chain reaction; PT — prothrombin time; TSH — thyroid stimulating hormone; USG — ultrasonography

Immune related adverse events associated with the endocrine system

Immune-related adverse events are relatively common in the endocrine system and it is important to note that in many cases they will persist after immunotherapy is completed. Usually it is associated with permanent damage to the endocrine gland or impaired function as a result of autoimmune reactions. The most common endocrinopathies are hypothyroidism or hyperthyroidism and hypophysitis. The damage rarely concerns multiple endocrine organs, however, this may make both the diagnosis and the treatment difficult, as hypophysitis, thyroiditis, or adrenalitis due to immunotherapy often give unspecific symptoms such as, for example, nausea and vomiting, headache, fatigue, or perturbed vision. It is also difficult to estimate the frequency of endocrinopathy occurrence because of different methods of evaluation, diagnosis, and monitoring in clinical trials. Symptoms that may suggest the development of endocrinological immunological toxicities are presented in Table 4.

Table 4. Symptoms suggesting the development of endocrinological immunological toxicities

Symptoms suggesting the development of endocrinological immunological toxicities
Headache
Perturbed vision
Tachycardia
Increased sweating
Fatigue or weakness
Muscle pains
Weight loss or gain
Dizziness or fainting
Changes in appetite (increased appetite or thirst)
Hair loss
Changes in mood or behavior, or amnestic symptoms
Chills
Constipation
Change in voice timbre
Polyuria
Nausea or vomiting
Abdominal pain

Hyperthyroidism/hypothyroidism

Thyroid function perturbations in the course of immunotherapy are the most common immunological complication concerning the endocrine system. They may take the form of hyperthyroidism or hypothyroidism, and in some cases the initial hyperthyroidism transforms into hypothyroidism. In most patients both hypothyroidism and hyperthyroidism are asymptomatic or show equivocal symptoms, requiring routine monitoring of biochemical blood parameters such as TSH, free triiodothyronine (fT3), and free thyroxine (fT4). Thyroid function (TSH, fT4) should be examined every 4–6 weeks during ICI treatment and continued every 6–12 months after termination of treatment.

Hypophysitis

Hypophysitis is a serious AE associated with immunotherapy as it may lead to considerable hormonal perturbations, including: secondary adrenal insufficiency caused by ACTH (adrenocorticotropic hormone) deficiency (adrenocortical insufficiency may require immediate medical attention), secondary hypothyroidism due to TSH deficiency or disorders due to follicle-stimulating hormone (FSH) and luteinizing hormone (LH) deficiency.

The most common hypophysitis symptoms are fatigue, nausea, vomiting, weakness, headaches, blurred vision, and perturbations of sexual functions (including loss of libido or menstrual disorders, or erection perturbations). Hypophysitis is diagnosed by analyzing concentrations of hormones produced by the hypophysis: low concentrations of ACTH, TSH, FSH, LH, growth hormone (GH), and prolactin, and by imaging studies, including MRI. MRI (preferably performed according to the pituitary protocol) may confirm immunological hypophysitis and exclude other causes of perturbations of the hypophysis, including metastases. Moreover, it should be noted that the results of assaying cortisol and ACTH may be perturbed if patients receive steroids at the beginning of treatment, for example, patients with lung cancer simultaneously receiving chemotherapy and checkpoint inhibitors with dexamethasone premedication.

Primary adrenal insufficiency

Adrenal insufficiency is rare during ICIs treatment. However, this is an emergency that requires prompt intervention. It may cause dehydration, hypotension and electrolyte imbalance (hyperkalaemia, hyponatraemia) up to an adrenal crisis. Intravenous corticosteroids and immediate hospitalization are recommended when an adrenal crisis is suspected.

Table 5. Indicated additional tests in patients with suspected/diagnosed immunological complications of the endocrine system

Laboratory tests
Complete peripheral blood count with differential white blood count
Creatinine, urea
ASPAT, ALAT
Bilirubin
Electrolytes (sodium, potassium, chlorine, calcium, magnesium)
Glucose
TSH, fT3, fT4
Laboratory tests for suspected hypophysitis or adrenal dysfunction
ACTH, FSH, LH, GH, prolactin, cortisol, IGF-1, testosterone (men), estradiol (women)
Test of adrenal reserve (test with Synacthen)
Imaging studies for suspected hypophysitis
Brain MRI according to pituitary protocol

ACTH — adrenocorticotropic hormone; ALAT — alanine aminotransferase; ASPAT — aspartate aminotransferase; GH — growth hormone; FSH — follicle-stimulating hormone; fT3 — free triiodothyronine; fT4 — free thyroxine; LH — luteinizing hormone; MRI — magnetic resonance imaging; TSH — thyroid stimulating hormone

Type I diabetes

Checkpoint inhibitor treatment is associated with an acute start of type I diabetes in about 0.2–0.9% of cases. Unfortunately, in many cases, patients have severe hyperglycemia or even ketoacidosis. However, some patients are asymptomatic, and some have symptoms such as fatigue, nausea, weight loss, polyuria, or polydipsia. All cases require insulin treatment from the moment of diagnosis and in general permanent insulin supplementation. Diabetes associated with ICI treatment may develop immediately after its initiation but also even a year later. Thus it is extremely important to monitor glucose concentrations at each dose of immunotherapy.

Indicated additional tests in patients diagnosed with/suspected of immunological complications associated with the endocrine system are presented in Table 5.

Immune related advers events associated with the respiratory system

Diagnosis of immune related pneumonitis (IP) is not easy. Both clinical and radiological symptoms are not characteristic and require differentiation from infectious pneumonia, progression of neoplastic disease, or pneumonitis due to radiotherapy. During periods of increased infections with the SARS-CoV-2 virus, differentiation between IP and COVID-19 with pneumonia may be problematic because of the similarity of clinical and radiological symptoms [21].

The symptom most commonly reported by the patients is dyspnea and coughing, less commonly other symptoms such as fever, pain, discomfort in the chest, tachycardia, a sensation of cardiac palpitations, or fatigue [22].

Over one-half of IP patients also have toxicity symptoms from other organs [23]. Importantly, IP is asymptomatic in one-third of the patients [23].

A preliminary imaging study is a chest X-ray that shows new pathological changes in the pulmonary parenchyma but does not allow the determination of their exact character. Radiological monitoring of the response to treatment using chest radiograms seems justified, especially in patients with a good general status or achieving a rapid clinical improvement, as it is an easily accessible analysis, it is cheap and is not a burden for the patient.

The basic radiological analysis in diagnosing IP is spiral chest CT with contrast. This allows evaluation of the character of the changes in lung parenchyma and the lymph node appearance and, therefore, is useful for differential diagnosis between IP and other possible causes of pathology mentioned above. IP appearance in a chest CT is not characteristic and most commonly has the form of consolidation and frosted glass but also it can look like organizing pneumonia, different interstitial lesions (thickening of interlobular septa, infiltration around bronchovascular bundles, subpleural reticular, and honeycomb lesions), pneumonitis with hypersensitivity with intralobular tumors, peribronchiolar infiltration, a tree with buds, or a combination of the above-mentioned images [22, 23]. If CT is the selected method of monitoring the response to treatment, a complementary method may be the use of high-resolution computed tomography, enabling a better, as compared to standard CT, evaluation of the character and intensity of interstitial lesions in patients with persistent radiological changes [24].

Laboratory analyses are helpful in differential diagnosis of other coexisting organ toxicities of immunotherapy. Immunological pneumonitis is associated with a moderate increase in C-reactive protein (CRP) concentration, and a decrease in CRP concentration correlates with response to treatment [25]. Therefore, additional laboratory tests (e.g., determining procalcitonin concentrations in serum) or bacteriological and virological analyses may be necessary to differentiate IP and pneumonia caused by an infectious agent.

In selected situations, bronchofiberoscopy with collection of biological material and/or bronchoalveolar lavage (BAL) are indicated. The BAL results from patients with IP are characterized by a higher percentage of lymphocytes [26]. Bronchoalveolar lavage may be used for bacteriological and mycological cultures and to check for infection with Pneumocystis jiroveci. An alternative material from the lower respiratory tract which is easier to obtain is sputum — a positive culture result indicates an infectious etiology.

Table 6. Additional tests in patients with suspected/diagnosed immune pneumonitis

Laboratory tests
CBC with differential
Creatinine, urea
ASPAT, ALAT
Bilirubin
CRP
Procalcitonin
TSH, fT3, fT4
Arterial blood gas analysis (alternatively arterialized capillary blood if artery cannot be punctured)
Imaging studies
Chest X-ray
Chest CT
Lung function tests
Spirometry
DLco
Body plethysmography
Bacteriological tests
Sputum culture
Culture of bronchoalveolar lavage
Blood culture
Assay for *Legionella* antigen in urine
Assay for *Streptococcus* antigen in urine
CR/antigen test for SARS-CoV-2 and influenza
Bronchofiberoscopy
Culture of bronchoalveolar lavage
Analysis of cellular content of bronchoalveolar lavage
Transbronchial lung biopsy

Necessary tests are bolded; ALAT — alaninę aminotransferase; ASPAT — aspartate aminotransferase; CBC — complete blood count; CT — computed tomography; CRP – C-reactive protein; DLco – diffusing capacity of the lung for carbon monoxide; fT3 — free triiodothyronine; fT4 — free thyroxine; RTG — X-ray; PCR — polymerase chain reaction; TSH — thyroid stimulating hormone

In particular cases, bronchofiberoscopy also allows collection of tissue material through transbronchial biopsy of suspicious radiological lesions. Histopathological analysis will allow the diagnosis of the type of pneumonitis (organizing pneumonia, granulomatous pneumonia, diffuse vesicular damage, or eosinophilic pneumonia) [27].

Functional lung tests, i.e., spirometry with evaluation of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco), should be performed in patients with established changes in the lung parenchyma. In patients with suspected perturbations of a restrictive type evidenced by spirometry, body plethysmography should be performed to detect lung parenchyma restrictions. Additional tests in patients with suspected/diagnosed immunological pneumonitis are presented in Table 6.

Table 7. Potential risk factors for the occurrence of cardiac toxicities in patients treated with immunotherapy [30]

Groups of risk factors	Risk factors
Factors directly associated with the type of treatment	• Combined immunotherapy: anti-PD-1 with anti-CTLA-4 (e.g. nivolumab with ipilimumab) • Immunotherapy combined with other cardiotoxic drugs (e.g. molecularly targeted treatment — VEGF tyrosine kinase inhibitors)
Current/prior cardiovascular system diseases	• Ischemic heart disease • Heart failure • Myocarditis • Status after myocardial infraction • Cardiac damage due to prior oncological therapy (e.g. chemotherapy with anthracyclines)
Autoimmunological disease (current and/or in history)	• Systemic lupus erythematosus • Rheumatoid arthritis • Sarcoidosis • Dressler syndrome
Immunological toxicities in other systems	• Immunotherapy-associated skeletal muscle inflammation
Neoplasm associated factors	• Cardiac antigens present in the tumor • Cardiac T-cell clones
Genetic factors	• Unknown

anti-CTLA-4 — anti-cytotoxic T lymphocyte antigen-4; anti-PD-1 — anti-programmed cell death 1; VEGF — vascular endothelial growth factor

Table 8. Additional tests in patients with suspected/diagnosed immunological toxicities concerning the cardiovascular system [30]

Cardiological evaluation of patients before initiating immunotherapy
History of prior diseases and evaluation of classical risk factors
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP) (to be considered)
Echocardiogram (to be considered)
Cardiological evaluation of patients from the high-risk group before and during immunotherapy
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP) before initiating immunotherapy and before the 2nd and 4th dose; then before the 6th and 12th, then every 3 administrations until completion of treatment
Consider echocardiography after 2nd or before 2nd dose and every 3–6 months in patients with initial damage to the left/right ventricle
Tests if new symptoms associated with the cardiovascular system appear e.g. chest pain, dyspnea, palpitations, fainting, loss of consciousness
ECG
Cardiac biomarkers (cardiac troponin and NT-proBNP)
Echocardiography
Cardiological consultation — always in the case of appearance of a new pathology in ECG, cardiac enzymes, echocardiogram

ECG — electrocardiography; NT-proBNP — N-terminal pro-B-type natriuretic peptide

Immunological complications related to the cardiovascular system

Immunological complications associated with the cardiovascular system are observed relatively rarely in the course of immunotherapy, but their consequences can be very serious, and in some cases, they may even lead to death. However, due to the high effectiveness of immunotherapy in treating patients with neoplasms, treatment should not be stopped without clear clinical evidence of the possibility of developing cardiac toxicity during immunotherapy as this could considerably worsen the patient's prognosis. Therefore, patients treated by immunotherapy should be under special cardiological supervision [28, 29].

The analysis of available trials indicates that the potentially increased risk of complications during immunotherapy is associated with the neoplasm, its prior or concomitant treatment, the status of the immune and cardiovascular systems, and most probably with genetic factors. Potential risk factors promoting higher frequency of adverse events during immunotherapy are presented in Table 7.

For cardiological supervision during immunotherapy, a preliminary evaluation is important which should include a detailed cardiological interview, measurement of basic heart functions (echocardiography — ECG), determination of basic biochemical parameters including cardiac troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP). The cardiac irregularities/diseases observed during the primary check-up should be clinically corrected or stabilized before initiating immunotherapy [30].

In supervising patients who are receiving immunotherapy, ECG, NT-proBNP, and cardiac troponin assays appear to be broadly accessible, most useful, and at the same time easy and least cumbersome. These are preliminary assays; if irregularities are observed in their values or clinical doubts arise, their broadening is indicated. It is very important to not only diagnose irregularities but also to compare them with the initial results (dynamics of changes), which facilitates therapeutic decisions. Determining cardiac troponin seems to be of particular importance, as it is a simple and specific marker of cardiac muscle [30–35]. Additional analyses in patients with suspected/diagnosed immunological toxicities concerning the cardiovascular system are presented in Table 8.

Conflict of interest

T.K.: fees for lectures from BMS, Gilead, Roche, MSD, AstraZeneca. Did not affect the content of this article.

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VIA MEDICA

ORIGINAL ARTICLE

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Microwave ablation of colorectal cancer lung metastases — the first experience in Poland

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ABSTRACT

Introduction. This study aimed to present the results of the first experiences in thermal ablation of colorectal cancer lung metastases in Poland.

Material and methods. Seven patients with colorectal cancer lung metastases were treated with CT-guided microwave ablation. One of them was lost to follow-up, so 6 patients with 7 metastatic foci were included in this study. The mean diameter of lesions was 15 mm (10–20 mm). The patients were disqualified from surgical treatment due to comorbidities.

Results. The mean duration of follow-up was 15 months (range: 6–29). No mortality was noted during that period. Local progression was not reported, while distant progression was found in two patients. Two patients presented with pneumothorax just after the ablation, and one of them required chest tube drainage. No complications were noted.

Conclusions. Patients with a few small colorectal cancer lung metastases can benefit from thermal ablation. The method is safe and should be available for medically inoperable patients with pulmonary oligometastatic disease.

Key words: colorectal cancer, lung metastases, interventional radiology, locoregional treatment, microwave ablation, lung ablation

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Introduction

Colorectal cancer is the third most commonly diagnosed malignancy and the second most common cause of cancer death [1]. The lung is the second (after liver) site of metastases for this malignancy with an incidence of around 10% [2]. For many years, patients with colorectal cancer and lung metastases have been considered to be in the end-stage of disease and were treated using only palliative therapy. In the 1990s, a concept of oligometastatic disease was presented [3]. It assumed potentially better survival rates if all foci of the disease would be removed in patients with a limited number of secondary deposits [4–6].

Resection is an established method of treatment of patients with colorectal cancer and pulmonary metastases [7], but there is a group of patients who are ineligible for surgery due to their comorbidities or limited pulmonary function. For these patients, stereotactic body radiotherapy is an optional treatment method; however, it has higher rates of local progression than the treatment of metastases from other sources [8].

Percutaneous computed tomography-guided thermal ablation has been used in the treatment of lung tumors since 1999 [9]. Since then it established its role in the treatment of patients with colorectal cancer lung metastases and is present in the international oncology guidelines [7, 10]. There is extensive evidence on

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Table 1. The results of microwave ablation of colorectal cancer lung metastases

Patient	Age	Tumor diameter	Lung segment	Follow-up (months)	Local progression	Distant progression
1	60	19	6L	8	0	1
2	60	12	6R	27	0	
2		13	3L	26	0	
3	79	16	4L	9	0	
4	78	20	8R	15	0	
5	50	16	4R	29	0	1
6	70	10	6L	6	0	

lung ablation efficacy [11], which is comparable with resection in terms of small (< 2 cm) lung metastases treatment.

Unfortunately, lung ablation is not widely available for patients in Poland due to the lack of reimbursement by the National Health Fund. The first attempts of performing this procedure started in academic and private healthcare in 2019. The purpose of this study is to present the results of the first experiences in thermal ablation of colorectal cancer lung metastases in Poland.

Material and methods

The Institutional Review Board waived the need for its formal consent due to the retrospective nature of this study. Seven patients with colorectal cancer lung metastases were treated with microwave ablation. One of them was lost to follow-up, and 6 patients with 7 metastatic foci were included in this study. One patient had single metastases in both lungs which were ablated in two separate procedures, 3 weeks apart. The remaining 5 patients had single metastases in one lung. There were 4 females and 2 males among the patients included in the study. The mean age of the patients was 56 years (50–79). The mean diameter of lesions was 15 mm (10–20 mm). Two patients had also single liver metastases that were treated during the same procedures. No extra-pulmonary metastases were visible in other patients. The patients were disqualified from surgical treatment due to comorbidities. Two patients had undergone lung surgery but were not fit for repeated resection.

The ablations were done with one of two microwave systems (Emprint, Medtronic, Minneapolis, MN, USA and Solero, Angiodynamics, Latham, NY, USA). All procedures were performed under general anesthesia with computed tomography (CT)-guidance (320-row CT scanner, Toshiba Aquilion One, Toshiba/Canon, Nasu, Japan). Contrast-enhanced CT was done immediately after each procedure to confirm the size of the ablation zone and to assess for possible complications. Chest x-ray was done 4–6 hours after ablation. The procedures were performed by three interventional radiologists with experience in CT-guided ablations. The follow-up protocol applied included CT exams at 6 weeks after ablation and, then, repeated every 3 months for at least 2 years.

Results

The mean duration of the follow-up was 15 months (range: 6–29). No mortality was noted during that period (Tab. 1). Local progression was not reported, while distant progression was found in two patients. Two patients presented with pneumothorax just after the ablation, and one of them required chest tube drainage. No complications were noted. No statistical analysis was performed due to the small number of patients included in the study.

Discussion

Thermal ablation of colorectal cancer lung metastases is an established method of treatment, especially in medically inoperable patients. This minimally invasive procedure is included in major oncological guidelines e.g. ESMO and NCCN [7, 10] as a method of management of such patients.

Local tumor progression

None of the patients in our study presented with local tumor progression. The results are in concordance with other publications. Kurilova et al. [12] reported local tumor progression-free survival rates of 93% (after 1 year) and 86% (after 3 years) while overall survival rates were 94% and 82%, respectively.

A prospective multicenter study by Hasegawa et al. [13] reported 3-year overall survival of 84% of participants and local progression-free survival of 91%.

This study included patients who underwent thermal ablation of colorectal cancer lung metastases with lesions measuring ≤ 3 cm in diameter. The results of the study are similar to publications on surgical resection reporting 3-year OS in the range of 71–82% [14, 15].

New metastases

Two patients in our study presented with new metastases in the lungs; however, they were ineligible for repeat ablation due to a large number of new lesions. Such disseminated progression is probably associated with more aggressive tumor biology because no local tumor progression was seen in these patients.

Tumor recurrence can be expected in over 50% of patients after pulmonary metastasectomy [16]. Repeat resection can be a valid option in some patients, but in many cases, it is not feasible, e.g. due to expected loss of pulmonary volume and function.

Lung preserving treatment is highly desirable in such patients. Unlike surgery [17] or radiotherapy [18], thermal ablation has no negative impact on pulmonary function [19].

The ability to repeat ablation in case of relapse is an important advantage of this method, as is the possibility of rapid assessment of treatment results (after 1 month). If a local relapse is reported, the lesion can be quickly re-ablated.

Complications

Pneumothorax occurred after 2 procedures; however, similarly to surgery, it should not be regarded as a complication but rather as an expected outcome of the procedure [20]. Having this in mind no major complications were noted. Low incidence of complications without any mortality is expected in CT-guided ablation of lung tumors [12].

Oligometastatic disease

Local treatment methods can be applied in the setting of oligometastatic disease, which is typically defined as the presence of 1–5 metastases in 1–2 organs. This concept is based on better survival rates of such patients if all metastases are resected or ablated [4, 5].

Metastasectomy is an effective method of colorectal lung metastases management [21] even though no randomized controlled trial is available to support data from other trials [22].

Still, only selected patients can undergo resection of colorectal lung metastases while repeat surgery is restricted to an even more exclusive group. For medically inoperable patients, ablation and radiotherapy are options of treatment.

Stereotactic body radiotherapy (SBRT) is one of the most frequently applied methods of treatment in medically inoperable patients. The efficacy of SBRT in terms of 3-year OS was reported by Agolli [23], Wegner et al. [24], and Yamamoto et al. [25] at 50.8%, 58%, 63.4% respectively. Relatively lower efficacy of SBRT in these studies is probably associated with radioresistance of colorectal cancer metastases compared to secondary deposits from other tumors — local progression rates are in the range of 42% *vs.* 16% [8]. According to the National Comprehensive Cancer Network (NCCN) guidelines, radiotherapy can be used in the treatment of such patients, however, its role is limited: "Conformal external beam radiation therapy may be considered in highly selected cases or the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable."

Still, SBRT is the only locoregional therapeutic option offered in Poland to medically inoperable patients with oligometastatic pulmonary disease in the setting of colorectal cancer.

Excellent results of many studies including the recent one by Hasegawa et al. [13], with 84% 3-year survival, support the need for wide access to thermal ablation for patients with colorectal lung metastases. This approach is supported by NCCN Colorectal Cancer guidelines v 2.2021: "Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of the disease need to be amenable to ablation or resection. Ablative techniques can also be considered when unresectable and amenable to complete ablation."

Limitations

The most important limitation of the study is the small number of patients. A relatively short follow-up period can also be a source of potential bias. The lack of data on the systemic treatment of these patients is also a limitation of this study.

Conclusions

The results of the study as well as other publications including current guidelines show that patients with a few small colorectal cancer lung metastases can benefit from thermal ablation. The method is safe and should be available for medically inoperable patients with pulmonary oligometastatic disease.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Benefits of β-blockers in cancer treatment

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ABSTRACT

Cancer is one of the leading causes of death in the world. Researchers keep attempting to develop therapy modalities to decrease the mortality and morbidity of cancer patients by trying to comprehend the effect of sympathetic nerves (through catecholamine and adrenergic receptors) in cancer development. Catecholamine activation in β-adrenergic receptors (β1-AR, β2-AR, and β3-AR) may influence cytokine and cancer immunity system, initiate tumorigenesis, stimulate tumor-associated macrophage and angiogenesis, influence tumor microenvironment, and facilitate cancer cell metastasis, leading to increased progressivity of cancer cells. β-blockers may inhibit catecholamine on β-AR and various types of paths needed for cancer cells to develop. β-blockers also stimulate cancer cell apoptosis, decrease pro-inflammatory mediators and growth factors of cancer cells. In addition, β-blockers also have benefits as supplementary cancer therapy, increase chemoradiotherapy sensitivity, decrease cardiotoxicity, and improve cancer cachexia. The benefits of β-blockers are expected to reduce morbidity and increase the survival rates of cancer patients. This review comprehensively assesses the benefit of β-blockers as a part of the complete management of cancer patients.

Key words: catecholamine, β-blockers, cancer, therapy

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Introduction

Cancer is one of the leading causes of death in the world. Global Cancer Statistic estimated there were 19.3 million of new cases, and 10 million deaths of cancer found in 2020. Various therapy modalities have been developed to reduce cancer mortality and morbidity rates, however, the results are still not satisfactory [1]. Current research focuses on studying the role of sympathetic nerves (through catecholamine and adrenergic receptors) in cancer development [2].

The role of catecholamine and adrenaline in cancer progression is related to their receptors. Neurotransmitters of catecholamine epinephrine (EP) and norepinephrine (NE) are related to α-adrenergic receptor (α-AR) and β- adrenergic receptor (β-AR) [3]. β-AR consists of 3 types, β1-AR, β2-AR, and β3-AR. β-AR exists in almost all normal tissues of the human body. Interestingly, β-AR (especially β2-AR) expression increases significantly on the surface of some types of primary cancer cells (most strongly in melanoma, breast, esophagus, pancreas) and metastasis cancer cells. Activation of β-AR by catecholamine modulates the progression and proliferation of tumor cells [4]. In addition, activation of β-AR regulates the cellular metabolic process, which is related to initiation and progressivity of cancer cells, including cell inflammation, tissue angiogenesis, cell apoptosis, cell communication and movement, repair of damaged DNA, cancer-related cellular immune response, and cell epithelial-mesenchymal transition [5].

β-blockers are the adrenoceptor antagonist which inhibits the β-AR receptor. β-blockers are an inexpen-

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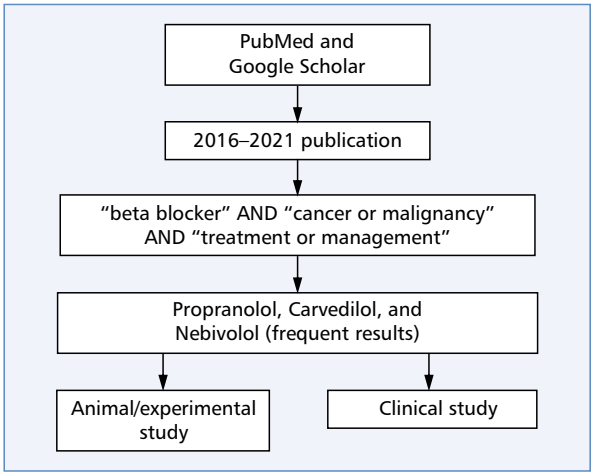

Figure 1. Flow chart illustrating article selection

sive drug, available throughout most of the world, with a relatively good drug safety profile [6]. β-blockers decrease the effect of catecholamine in human body cells [7]. Inhibition of beta-AR blockers slows down the progressivity of cancer progressivity of cancer and increases the survival rate of cancer patients [8]. The other beneficial effect of β-blockers is to prevent chemotherapy's side effects and increase the sensitivity of cancer cells to chemotherapy [9, 10]. The advantages of β-blockers as therapy in cancer management need to be studied further.

Methods

This literature review aimed to review recent developments and publications concerning the role of the *β-blocker* in cancer treatment. We reviewed all publications from the database of PubMed and Google Scholar published between 2016–2021 as illustrated in Figure 1. Older articles are included if they provide important information. First, we used the terms "catecholamine" AND "cancer or malignancy." Then, we continued using the terms "beta blocker" AND "cancer or malignancy" AND "treatment or management." We also searched for other specific keywords, such as "chemo-radiotherapy" OR "cardiotoxicity" OR "cancer cachexia" OR "survival."

Results

Catecholamine influences cytokine and cancer immune system

Catecholamine released during chronic stress influences immune response [11]. Stimulation of catecholamine on β-AR causes macrophage polarization (Fig 2.) and cytokine production and gives rise to the development and progressivity of breast cancer [12].

Chronic activation of β-AR signal on mice suppresses the activity and number of natural killer cells (NK cell), increasing the risk of cancer cell metastasis [13]. Activation of the β-AR signal also increases the expression of the anti-apoptotic protein molecule (BAD, BCL-2, and MCP-1) on tumor cells. Norepinephrine activates the path of transforming growth factor β (TGF-β) in cancer cells and increases the capability of distant metastasis [11, 14]. Norepinephrine also increases the chemotaxis ability of breast cancer cells for distant metastasis mediated by chemokine [15].

Catecholamine stimulates polarization of macrophage M2

The activation of β-AR by catecholamine strongly stimulates macrophage to polarize into macrophage M2 (Fig. 2). Stimulation of β-AR can reverse M1-like macrophages into M2. Decreasing the content of catecholamine in the body may reduce the polarization of macrophage into M2. M2 exists in a large number around tumor cells along with growing new tiny blood vessels that support the life of tumor cells [12, 16].

Catecholamine triggers tumorigenesis

DNA damage may trigger tumor formation [17]. The direct effect of catecholamine on cancer cells is to promote tumorigenesis, tumor cells proliferation, anti-apoptotic, and promote metastasis through the DNA damage pathway [18, 19]. The effect of catecholamine on β2-AR increases the degradation of p53 and causes DNA damage. This process occurs through arrestin beta 1 (ARRB1) pathways, protein kinase A (PKA), and activation of proto-oncogene Src and Her2 [20, 21].

Chronic activation of adrenoceptor by G-coupled protein may induce normal cells to have malignant transformation [22]. Prolonged exposure of norepinephrine and epinephrine to NIH3T3 cells (experiment mouse fibroblast cell) and murine 3T3 cells increases DNA damage, cell proliferation rate, and tumor formation. This shows that the normal cellular genes act as a proto-oncogene, which is the initial stage of tumor formation [20, 23]. Activation of PKA by β2-AR receptor will result in reactive oxygen species (ROS) which damages DNA. This study demonstrates that catecholamine induces DNA damage in normal cells and triggers cancer cell development [21].

Other evidence states that norepinephrine induces phosphorylation of voltage-dependent calcium channels (VDCC) L-type through the β-adrenergic receptor (β-AR) -PKA pathway. VDCC triggers calcium mobilization, inducing activation of IGF-1R through exocytosis of insulin-like growth factor (IGF2). Mice expressing

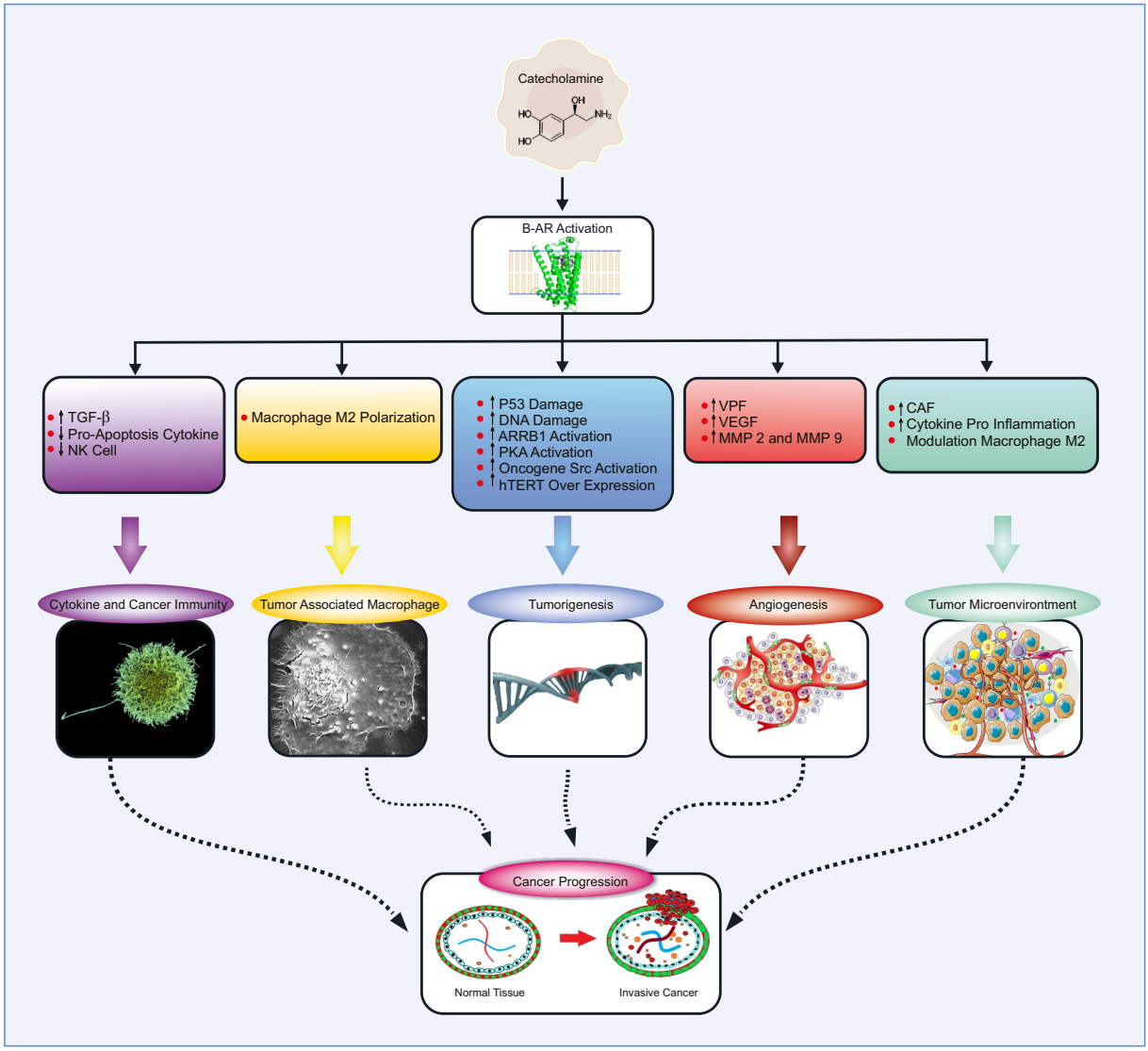

Figure 2. Catecholamine action towards cancer progressiveness; TGFb — tumor growth factor beta; NK cell — natural killer cell; ARRB — arrestin beta 1; PKA — protein kinase A; VPF — vascular permeability factor; VEGF — vascular endothelial growth factor; CAF — cancer-associated fibroblasts; hTERT — human telomerase reverse transcriptase; MMP — matrix metalloproteinase

lung-specific IGF-1R show faster development of lung tumors [24]. Norepinephrine also stimulates the expression of human telomerase reverse transcriptase (hTERT), which initiates cancer formation through epithelial-mesenchymal transition (EMT) [25].

Catecholamine influences angiogenesis

β-AR (β1-AR, β2-AR, and β3-AR) subtypes are expressed on the blood vessel of tumor tissue [26]. β2-AR activation by catecholamine on tumor cells increases the formation of proangiogenic factors [27]. Norepinephrine activates cAMP-protein kinase A (PKA), increases vascular permeability factor/vascular endothelial growth factor-A (VPF/VEGF) synthesis, and expression of matrix metalloprotease 2 (MMP 2) and MMP 9 are increased [28]. β2-AR also stimulates activation of Epac1 (exchange factor directly activated by cAMP1) and PKA that will increase vascular endothelial growth factor (VEGF) [29].

Activation of noradrenaline on β2-AR of endothelial cells is important to start the angiogenic process that triggers tumor cell growth. The removal of β2-AR on endothelial cells inhibits metabolic changes needed by the cancer cell angiogenesis process. Oxidative phosphorylation and formation of mitochondrial cytochrome C are also increased, and thus they inhibit angiogenesis and cancer cell growth [30].

Catecholamine influences tumor microenvironment

Neurotransmitter catecholamine of sympathetic nervous system modulates bone marrow cell microenvironment, thus increasing cancer cell progressivity [31]. Norepinephrine, through β3-AR, increases cancer-associated fibroblasts (CAF) activation, maintains pro-inflammatory cytokine secretion, which is important to maintain the tumor microenvironment. β3-AR also stimulates the mobilization of precursor cells (mesenchymal stem cells and endothelial precursor cells) of bone marrow into tumor cells. The precursor cells become adult CAF, which supports the inflammatory and angiogenesis processes of tumor cells [32]. β3-AR activation causes cancer cells to be more sensitive to environmental stimulation, namely hypoxia, nutritional availability, CAF count, and cancer-associated macrophages (CAM). The cascade described is like a vicious circle that will repair the microenvironment, inflammatory process, and cancer cell angiogenesis [33, 34].

Catecholamine also influences stromal cell-derived factor 1 (CXCL12) that serves to change the hematopoietic stem and progenitor cells (HSPCs) and bone marrow homing process. The microenvironment change is preferred as a place for cancer cell metastasis [35].

Catecholamine's role in cancer pathogenesis, as stated earlier, is that it influences cancer growth and development. Catecholamine action towards cancer progressiveness is presented in Figure 2. Inhibition of catecholamine receptors is also deemed to influence cancer progressivity. Thus, β-blockers, as the agonist of β-AR adrenoceptor, can be used to inhibit cancer development.

Effect of β-blockers on cancer

Denervation of tumor tissue stops catecholamine flow on β-AR in cancer cells, inhibiting the growth and spread of cancer cells. Administrating β-blockers also causes denervation of tumor tissue and inhibits the growth and spread of cancer cells [36, 37]. Catecholamines influence cancer development through their activity at β adrenergic receptors (β-AR 1, β-AR 2, and β-AR 3) [38]. In this article, we divide β-blockers (traditionally) into non-selective β-blockers and selective β-blockers. We used propranolol, carvedilol, and nebivolol as sample drugs in this study because they are representative of each type of β-blocker, and they are widely used in clinical practice and appear in our study search results. Propranolol represents an older non-selective β-blocker. Carvedilol represents a newer non-selective β-blocker. Nebivolol represents a selective β-blocker.

In this article, we divide the effect of β-blockers on cancer into experimental (*in vitro*) and clinical studies.

Effects of non-selective β-blockers in experimental cancer studies

Propranolol

The propranolol inhibition on β-AR is not selectively limited. This is beneficial since propranolol can inhibit catecholamine effects in every adrenergic receptor (β1-3AR) expressed by various cancer cells [4, 5].

Propranolol administration in an in-vitro study to some cancer types shows an inhibitory effect in various types of metabolic paths of cancer cells. Propranolol stimulates activation of poly (ADP-ribose) polymerase (enzyme serving to repair DNA, genome stability, and cell apoptosis) in liver cancer. Propranolol stimulates liver cancer cell apoptosis by influencing the expression of enzyme caspase-3 (the enzyme which disturbs the cell cycle until ceasing in phase S) [39]. Administration of propranolol to squamous cell carcinoma, induced by norepinephrine, decreases the cancer migration and invasion ability [40].

Melanoma patients present a good response to propranolol treatment [41, 42]. Propranolol decreases the level of VEGF, which plays a role in angiogenesis in melanoma cases. Propranolol also stimulates melanoma cell apoptosis by inducing phase G0/G1/S through the PKB/MAPK (protein kinase B/mitogen-activated protein kinase) pathway [43]. Ovary cancer cell apoptosis is stimulated by propranolol through inhibiting the cell life cycle at phase G2/M. The protein content of beclin-1 and p62 that stimulates the process of autophagy of ovary cancer cells is also increased by propranolol [44].

The administration of propranolol in in-vitro research of colorectal cancer cells decreases the level of Hypoxia-Inducible Factor1 α (HIF1α) and carbonic anhydrase IX (CA-IX). CA-IX is a protein that repairs the microenvironment of cancer cells and improves cancer cells for distant metastasis. Propranolol reduces the amount of protein involved in oxidative phosphorylation, which may potentially reduce the risk of distant metastasis in colorectal cancer cells [45].

Propranolol can process immunomodulatory cellular immune responses related to cancer. Propranolol increases IL-2, IL-4, IL-12, IL-17, and IFN-γ cytokines that can suppress breast cancer in experimental studies on animals [46]. Propranolol increases the number of CD 8+ cells and the expression of GzmB/IFN-γ/T-bet on CD 8+ cells in colon cancer tissue of experimental mice [47].

Carvedilol

Research on carvedilol as cancer therapy until recently has remained in vitro. Skin cancer model cells, JB6P+, show high expression of β2-AR. The administration of carvedilol may inhibit epidermal growth factor (EGF) and activator protein (AP1) needed by JB6P+

Table 1. Summaries of β-blockers benefit in inhibiting cancer progression (*in vitro* study)

Ref.	Drugs	Type of cancer	Mechanism	Outcome
[39]	Propranolol	Liver Cancer	↑ ADP-ribose polymerase cleavage ↑ induced S-phase arrest ↓ the expression of caspase-3	↑ apoptosis in liver cancer cell
[40]	Propranolol	Squamous Cell Carcinoma	↓ norepinephrine effects	↓ cell migration and invasiveness
[44]	Propranolol	Ovarian Cancer	↑ cell cycle arrest ↑ phosphorylation of JNK	induced cell cancer apoptosis and protective autophagy
[45]	Propranolol	Colon Cancer	↓ levels of HIF1α and carbonic anhydrase IX ↓ proteins in oxidative phosphorylation	↓ metastatic potential ↓ cells viability and proliferation
[46]	Propranolol	Breast cancer	↑ immunomodulatory cellular immune responses related to cancer ↑ IL-2, IL-4, IL-12, IL-17, and IFN-γ	↑ cellular immunity against cancer
[47]	Propranolol	Colon cancer	↑ CD 8+ cells ↑ expression of GzmB /IFN-γ/ /T-bet on CD 8+ cells	↑ cellular immunity against cancer
[48]	Carvedilol	Skin Cancer	↓ EGF ↓ activator protein-1	↑ skin cancer chemoprevention
[50]	Carvedilol	Skin Cancer	↓ UV-induced AP-1 and NF-kB activity.	↓ inflammatory activity skin cancer ↓ malignant transformation of skin cells
[51]	Carvedilol	Mammary Epithelial Cells	↓ ROS-mediated phosphoinositide 3-kinase/protein kinase B signaling	↓ the malignant proliferation of mammary epithelial cells
[52]	Nebivolol	Unspecific Cancer Cell	↓ mitochondria respiration ↓ oxidative phosphorylation ↓ ATP synthase activities ↓ VEGF	↓ tumor growth and tumor angiogenesis
[53]	Nebivolol	Oral squamous cell carcinoma	↑ endoplasmic reticulum stress ↑ expression of inducible nitric oxide synthase	↑ mitochondrial dysfunction and cancer cell growth arrest

cells to transform into malignant cells [48]. Carvedilol reduces anti-inflammatory activity by attenuating UV-induced AP-1 and NF-kB activity. It may inhibit the malignant transformation of skin cells because of exposure to ultraviolet light [49, 50].

Ductal carcinoma by exposure to strong carcinogen benzo(a)pyrene can be prevented by carvedilol through inhibition of ROS production which stimulates activation of the PI3K/AKT signal pathway (important signal of excessive cell growth) [51].

Effects of selective β-blockers in experimental cancer studies

Nebivolol

Research on selective β-blockers in inhibiting cancer progression in vitro is still very limited. In our search, nebivolol was a selective β-blocker that was frequently used in studies (though it is still rare). Nebivolol is a selective inhibitor of β1-AR and has a good effect on certain types of cancer. Nebivolol inhibits the use of glucose and palmitate in mitochondrial respiration of colorectal cancer, breast cancer, lung cancer, and ovary cancer cells. The utilization of inhibited glucose causes cancer cells not to produce ATP needed for cancer cell development [52]. Nebivolol downregulates VEGF2 receptor expression, needed in endothelial cell proliferation, inhibiting the cancer cell angiogenesis process. The life cycle of cancer cells is stopped by nebivolol by preventing activation of extracellular signal-regulated kinase (ERK) participating in cell cycle phase S [52]. In oral squamous cell carcinoma, nebivolol activates the endoplasmic reticulum (ER) stress signaling pathway by increasing the expression of inducible nitric oxide synthase. ER stress triggers mitochondrial dysfunction and cell growth arrest [53]. Only a few research studies have been conducted related to selective β-blockers on cancer cases since the inhibition is specific only to β1-AR. Summaries of β-blockers' benefits in inhibiting cancer progression are presented in Table 1.

Effects of non-selective β-blockers in clinical cancer studies

Propranolol

Propranolol is useful and shows good results in patients with various types of breast cancer. Propranolol administered to early-stage breast cancer patients, downregulates the expression of protein pro-proliferative Ki-67. Phosphorylation of mediator regulating splitting of cancer cells (p44/42 MAPK, p38 MAPK, JNK, and CREB) lower, while phosphorylation of mediator stimulating cancer cell apoptosis (AKT, p53, and GSK3β) increases [54].

Propranolol administered as adjuvant therapy to late-stage breast cancer patients (stage 3 or higher) downregulates the expression of protein pro-proliferative Ki-67 and protein pro-survival Bcl-2 and increases the expression of protein pro-apoptotic p53. Propranolol is useful to deal with local and far-spread breast cancer cells [55].

The use of propranolol before diagnosis reduces the risk of cancer stage progression compared to patients without a propranolol use history. The breast cancer-specific mortality level also decreases significantly for patients who use propranolol [56]. Propranolol administration 7 days before breast cancer operation, reduces the biomarker of pro-metastatic inflammation (Activator protein-1, Snail/Slug, NF-KB/Rel) [57]. Meanwhile, propranolol administration to triple-negative breast cancer patients increases recurrence-free survival and reduces metastasis risk. Progression-free survival of HER2-negative breast cancer patients in the late stage is better with propranolol administration. Propranolol also improves the sensitivity to trastuzumab therapy for HER2-positive breast cancer patients [58].

Propranolol administration in combination with etodolac perioperative (20 days) improves colorectal cancer marking molecules, covering reduction of epithelial to mesenchymal transition, tumor-infiltrating CD14+ monocytes, and CD19+ B cells, and increases the number of tumor natural killer cells CD56+ [59]. Propranolol prolongs time-to-discontinuation of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and improves the overall survival of lung adenocarcinoma patients receiving first-line EGFR-TKIs therapy [60]. Propranolol also improves the overall survival of unresectable hepatocellular carcinoma patients [61].

Carvedilol

In a population-based study, long-term use of carvedilol has been shown to reduce the risk of gastric and lung cancer [62]. Nonselective β-blockers (including carvedilol) reduce the incidence of hepatocellular carcinoma in patients with liver cirrhosis [63]. Carvedilol also blocks neural regulation to reduce cancer-specific mortality in breast cancer [64].

Effects of selective β-blockers in clinical cancer studies

Our search shows that clinical studies of nebivolol are still limited. The benefits of selective β-blockers remain in the area of cardiotoxicity induced by chemo-radiation therapy (as mentioned in Table 2).

β-blocker administration does not only affect cancer progressivity in clinical cancer studies but also serves as an adjunctive for conservative clinical cancer therapy.

β-blockers increase the sensitivity of cancer cells to chemo-radiotherapy

Chemo-radiotherapy is the modality commonly used in cancer patient treatment. Stimulation of catecholamine increases cancer cell progressivity and may reduce the effect of chemotherapy drugs, such as doxorubicin, on cancer cells. Inhibition of doxorubicin's efficacy occurs through increasing expression of silent information regulator1 (Sirt-1) by catecholamine stimulation [10].

Administration of β-blockers increases the sensitivity of lung cancer cells to radiotherapy and drug cisplatin. Propranolol in combination with radiotherapy or cisplatin reduces the expression of phosphoprotein kinase A(p-PKA) that inhibits the survival of the clonogenic cells of lung adenocarcinoma compared to radiotherapy or cisplatin only [65]. The administration of propranolol to sarcoma increases the sensitivity to doxorubicin by changing drug metabolism in intracellular lysosomes. Propranolol inhibits the pump that releases doxorubicin to extracellular, increasing the level of intracellular doxorubicin and the ability of doxorubicin to damage the DNA of cancer cells [66]. Propranolol also increases the sensitivity to doxorubicin in myeloid leukemia cells [67].

Propranolol administered to experimental mice, increases the sensitivity of stomach cancer cells to radiotherapy. Propranolol reduces the expression of NF-κB, EGFR, VEGF, COX-2 in stomach cancer cells, becoming more sensitive to radiotherapy [68]. Propranolol and carvedilol can significantly reduce the number of fractions of a dog's osteosarcoma cells after 3 Gy radiation [69].

β-blockers increase the effectiveness of immune checkpoint inhibitors

β-blockers also serve to increase the effectiveness of immunotherapy. CD8+ cytotoxic T lymphocytes (CTLs) are one target of treatment through immune checkpoint

Table 2. Summaries of β-blockers benefit in clinical cancer study (in vivo study)

Ref.	Drugs	Type of cancer	Mechanism	Outcome
[54]	Propranolol	Early-stage breast cancer	↓ protein pro-proliferative Ki-67 ↓ Phosphorylation of mediator regulating splitting of cancer cells (p44/42 MAPK, p38 MAPK, JNK, and CREB) ↑ phosphorylation of mediator stimulating cancer cell apoptosis (AKT, p53, and GSK3β)	Reduces tumor proliferative index
[55]	Propranolol	Late-stage breast cancer	↓ protein pro-proliferative Ki-67 ↓ protein pro-survival Bcl-2 ↑ expression of protein pro-apoptotic p53	↓ cancer cell cycle progression ↑ cell apoptotic
[56, 58]	Propranolol	Breast cancer	–	↓ metastasis development ↓ tumor recurrence ↑ disease-free interval
[59]	Propranolol with etodolac	Colorectal	↓ epithelial to mesenchymal transition ↓ tumor-infiltrating CD14+ and CD19+ B cells, ↑ tumor natural killer cells CD56+	Improve colorectal cancer marking molecules
[60]	Propranolol	Lung adenocarcinoma	–	↑ time-to-discontinuation (EGFR-TKIs) and ↑ overall survival of lung adenocarcinoma
[62]	Carvedilol	Gastric and lung cancer	–	↓ risk of gastric and lung cancer
[63]	Nonselective β-blockers (including carvedilol)	HCC	–	↓ incidence of HCC in liver cirrhosis
[64]	Carvedilol	Breast cancer	Blocks neural regulation	↓ cancer-specific mortality ↓ Tumor growth

HCC — hepatocellular carcinoma

inhibitors (ICI). The lymphocyte cells kill cancer cells that represent major histocompatibility complex molecules MHC class 1 [70]. On the other hand, activation of β-AR in CD8+ CTLs cells reduces cells' ability to kill cancer cells, reducing interferon proliferation and production ability. The administration of β-blockers increases CD8+ CTLs count [71]. Non-small cell lung cancer patients receiving ICI therapy in combination with β-blockers show improved progression-free survival [72].

β-blockers prevent cardiotoxic effects of chemo-radiotherapy

Anthracycline is a chemotherapy drug with a cardiotoxic effect. Anthracycline causes increased reactive oxygen species (ROS) accumulated in cardiac muscle mitochondria [73]. β-blockers (carvedilol and nebivolol) serve as an antioxidant that reduces oxidative stress in cardiac muscle, preventing damage to the heart because of anthracycline [74, 75].

Carvedilol prevents reduction of left ventricular ejection fraction (LVEF), prevents diastolic dysfunction, and cardiac remodeling. Carvedilol reduces markers of heart damage in patients receiving anthracycline or trastuzumab therapy [76–79].

Nebivolol prevents reduction of myocardial velocities and deformation of the ventricular muscle structure of breast cancer patients receiving doxorubicin therapy [80]. This protective effect is caused by its ability to modulate caspase-3, e/i NOS, and TNF alpha that prevents apoptosis in cardiac muscle [81]. Nebivolol also increases nitrite oxide content serving as an antioxidant [82].

Radiotherapy in the breast area can also cause cardiotoxicity. This damage includes cardiomyopathy, acceleration of formation of atherosclerosis, fibrosis pericardial valve and tissue, and cardiac conduction disorder [83]. These damages can generally be treated using β-blockers [84, 85].

Table 3. Summaries of β-blockers improve cancer survival

Ref.	Drugs	Type of cancer	Type of study	Outcome
[93]	β-blocker	–	Systematic review and meta-analysis	↓ all-cause mortality
[94]	β-blocker	–	Meta-analysis	↑ overall survival ↑ disease-free survival
[95]	β-blocker	Ovary cancer, pancreas cancer, breast cancer, and melanoma	Meta-analysis	↑ cancer-specific survival
[96]	β-blocker	Breast cancer	Retrospective	↑ disease-free interval
[61]	Propranolol	Unresectable HCC	Population-based study	↓ mortality risk

HCC — hepatocellular carcinoma

β-blockers prevent cancer cachexia

There is currently no specific therapy for cancer cachexia. One modality proposed as cancer cachexia therapy is to administer β-blockers [86, 87]. Cancer cachexia, besides extremely reducing muscle mass, also causes a reduction of cardiac muscle mass (cardiac cachexia). Cardiac cachexia makes it more difficult to treat the effect of chemotherapy-induced cardiotoxicity [88, 89]. β-blockers (particularly selective β1-blockers) prevent worsening cardiac cachexia [90, 91]. Espindolol increases body weight and body fat proportion in colorectal and lung cancer patients. The effect of Espindolol is related to its ability to reduce metabolism (nonselective inhibition on β-AR), reduce fatigue and thermogenesis (as an agonist of central 5-HT1α receptors), and pro-anabolic effect (as a partial agonist of β-2 receptors) [92].

β-blockers and cancer survival

Our review shows that β-blockers, especially nonselective β-blockers, are beneficial in improving overall survival by preventing cancer progression and as adjunctive therapy to conventional cancer therapy (as listed in Table 3). However, studies are not consistent in showing that β-blockers have improved overall survival (OS).

Meta-analysis research shows that β-blockers reduce the hazard ratio of all-cause mortality of cancer patients [93] and increase the overall survival and disease-free survival of cancer patients (particularly ovary cancer, pancreas cancer, breast cancer, and melanoma) [94, 95]. Administration of β-blockers to breast cancer patients significantly reduces metastasis occurrence, cancer recurrence, and longer disease-free intervals [96].

The research conducted by Na et al. states, conversely, that there is no evidence showing the correlation between the use of β-blocker and overall survival, all-cause mortality, disease-free survival, progression-free survival, and recurrence-free survival for cancer patients. The varied results are caused by different study designs, different drug working methods, type and stages of cancer, too heterogeneous sample population, and time of β-blocker administration [93, 97]. The other reasons are due to the progression of cancer through various molecular pathways, not only through the catecholamine pathway [98, 99]. In addition, many exogen factors affect cancer mortality/overall survival (i.e depression, economy, delayed treatment, surgery, nutrition) [100]. Another confounder that may influence the difference in the result of research on β-blockers in the survival of cancer patients is immortal time bias (ITB). ITB may cause the result of survival-related research to seem better. Meta-analysis and systematic review researches excluding ITB influence in their studies on the influence of β-blockers on cancer survival show insignificant results [101, 102].

Conclusion

Administrating β-blockers inhibits catecholamine activation through β adrenoceptors (β1-AR, β2-AR, and β3-AR), so that cancer cell formation, progression, and metastasis are inhibited. β-blockers are also useful as adjunctive therapy to prevent cancer cachexia, chemoradiotherapy-related cardiotoxicity, and can increase the sensitivity to immune checkpoint inhibitors and chemoradiotherapy. The benefits of β-blockers will be stronger when they are applied to cancers that strongly express β adrenergic receptors (e.g. melanoma, breast cancer). Non-selective β-blockers are superior to selective β-blockers since they block all three types of β adrenergic receptors.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Radioligand therapy — personalized treatment for patients with neuroendocrine tumors

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ABSTRACT

Over the past 2 decades, radioligand therapy (RLT), previously referred to as peptide receptor radionuclide therapy, has been proven to be an effective and safe therapeutic option in patients with advanced, unresectable, often progressive, well-differentiated neuroendocrine tumors. The NETTER-1 study, the only randomized phase-III trial to date, established RLT with 177Lu-DOTATATE as the "gold standard" in the treatment of metastatic or locally advanced tumors, which are unresectable, well-differentiated with somatostatin receptor (SSTR) expression, and progressive neuroendocrine tumors.

Key words: neuroendocrine tumours (NET), radioligand therapy (RLT), peptide receptor radionuclide therapy (PRRT), somatostatin receptor overexpression

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Introduction

In the era of personalized medicine, new targets localized on the surface of neuroendocrine tumors have been used for radioligand therapy (RLT).

During the last 2 decades RLT, previously described as peptide receptor radionuclide therapy (PRRT), has proved to be an effective and safe therapeutic option in patients with advanced, unresectable, often progressing, well-differentiated (NET neuroendocrine [NET]) tumors [1–6].

This form of molecularly directed therapy, or RLT/PRRT, is based on the use of a synthetic somatostatin analogues (SSA) linked by a so-called linker-chelator (the most currently used substance is DOTA) with an appropriate radioactive isotope (radioisotope). This therapy can be used in patients with well-differentiated neuroendocrine tumors, which are characterized by overexpression of the somatostatin receptor (SSTR). The therapy aims to provide permanent binding of the prepared complex of the radioisotope and somatostatin analog with the receptor on the surface of the tumor cell and irradiate it with high-energy electrons originating from beta decay within the atomic nucleus. The binding of the analog complex and the radioisotope with the membrane receptor does not have to be associated with the internalization of the formed ligand-receptor complex to the interior of the cell as just the permanent binding of the radiopharmaceutical to the receptor causes irradiation of the tumor cell and additionally of neighboring cells [1, 4–6]. The range of this corpuscular irradiation is, at most, several millimeters. This distance is sufficient for damaging many tumor cells, with practically minor damage to tissues adjacent to the tumor. Additionally, this type of therapy is currently characterized by low, manageable adverse effects and toxicity.

The success of this therapy and its position in the current algorithm of treating well-differentiated neuroendocrine neoplasms (NEN) depend on the selection

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of patients, appropriate imaging markers qualifying for RLT, and an appropriate structural, functional, and clinical evaluation of the response to treatment [1, 7].

The synthetic somatostatin receptor ligand (SRL) labeled with high doses of the Indium-111 radioisotope was the first radiopharmaceutical that was used in NET therapy. The high activities of 111In-DTPA-Octreotide used during therapy yielded encouraging results in the control of the symptoms of well-differentiated secreting NET. However, objective responses were rare, and hematological adverse effects were also observed [8].

Next new analogs labeled with β-emitting radionuclides were introduced: Yttrium-90 (^{90}Y) and Lutetium-177 (177Lu). During the next 15 years in many retrospective and prospective phase I, II studies using both radiopharmaceuticals and various types of synthetic SRL, disease control rate (DCR) at the level of 68–94% was observed in patients with various types of neuroendocrine tumors, as well as significant prolongation of overall survival (OS) and progression-free survival (PFS,) [6, 9–11]. Biochemical and clinical responses were also observed in the form of decreased symptoms of hormone hyperactivity and improved quality of life [12].

Data concerning PRRT safety are also encouraging for the use of this form of therapy [6, 13–15]. The most common acute adverse effects are nausea and vomiting, mainly associated with amino acid infusions (AA), which are supposed to protect against RLT nephrotoxicity. Among other adverse effects, the following should be mentioned: fatigue, general malaise, sporadic stomach pains, and transitory lymphopenia, which are generally mild, self-limiting, and reversible. Breakthrough carcinoid syndrome during therapy in the case of hormonally active NET originating most commonly from the midgut is a very rare complication. Nephrotoxicity is a late adverse effect of PRRT mainly when ^{90}Y is used. Based on long-term observation of patients participating in the NETTER-1 trial, the frequency of occurrence of strong nephrotoxicity in patients treated with ^{177}Lu--DOTATE was low (5%) and similar to that observed in the control group (4%). Comparable changes in creatinine clearance in a defined time in both studied groups suggest that there is no detrimental, long-term effect of ^{177}Lu-DOTATE on kidney function in patients in the arm with RLT [16].

Hematological toxicity, such as acute lymphoblastic leukemia (ALL) or myelodysplastic syndrome (MDS), was observed in less than 5% of patients who received PRRT [13, 14].

Preliminary phase I and II clinical trials on using RLT in various types of NET were successful. However, only the NETTER-1 trial published in 2017 established PRRT using ^{177}Lu-DOTATATE as a standard of care in treating patients with metastatic or locally advanced well-differentiated progressing NEN with the expression of the somatostatin receptor [15].

The basis of radioligand therapy — RTL/PRRT

As mentioned above, RLT/PRRT using radioisotope labeled somatostatin analogs (SSTA) is a reasonable option in treating unresectable and/or metastatic well/moderately differentiated NET [1–7]. The main aim of this therapy is to provide a high dose of corpuscular beta radiation, and currently in the phase of clinical trials, also radionuclides with alpha decay, to tumor cells and to obtain the effect of a cross-fire directed at nearby cells. Due to this phe nomenon, the therapy additionally encompasses cells with a low expression of the SST receptor or its absence in the case of a heterogeneous distribution of the receptor on the NET surface. Because of the range of this irradiation, the total dose absorbed by normal tissues surrounding the tumor is significantly decreased. In the case of the currently commonly used lutetium (^{177}Lu), the majority of the electrons derived from radioactive decay have a range below 1 mm.

Synthetic somatostatin analogs labeled with a radioisotope are used by their systemic administration in fractionated doses and sequential cycles (generally 4) every 6 to 9 weeks [1–7]. The potential risk of damage to the kidney and bone marrow limits the cumulative dose of radioactivity that can be administered to the patient [12].

Generally, the response to treatment is associated with the initial very high accumulation of the radiopharmaceutical in somatostatin receptor imaging (SRI) performed by single-photon emission computed tomography (SPECT/CT) using, for example, ^{99m}Tc HYNICTOC or by PET/CT employing analogs of the SST receptor labeled with ^{68}Ga DOTATATE/DOTATOC [1, 2]. The effectiveness of the therapy is associated with the high affinity of the used radiopharmaceuticals for somatostatin receptors mainly of subtype 2 (sst2) and moderate affinity for subtype 5 (sst5) and other SSTR subtypes. The response also depends on the tumor mass, the biology of its cells with a potentially high index of resistance, and the high absorbed dose of energy deposited inside neoplastic cells with high SSTR expression [4, 5, 8].

The next factor affecting the effectiveness of therapy is the choice of the type of radionuclide. Each of the β emitters currently used in therapy — ^{177}Lu and ^{90}Y, has its advantages. In particular ^{90}Y electrons have high energy (Emax 2.27 MeV, penetration range R_{max} 11 mm, halflife $T_{1/2}$ 64 hours) and are characterized by a higher range of penetration within the tumor, which leads to greater irradiation of larger lesions with a heterogeneous accumulation of the radiopharmaceutical. The cross-fire phenomenon also occurs.

The shorter half-life of ^{90}Y contributes to decreasing its toxicity in respect to sensitive organs such as bone marrow and kidneys. In turn, ^{177}Lu has lower energy

and thus the range of beta irradiation, which allows better deposition of energy in the case of smaller tumors. An advantage of ^{177}Lu is also its lower toxicity for bone marrow and kidneys in comparison to ^{90}Y [2, 12, 13].

Prognostic and predictive factors of RLT

In the context of RLT, the degree of differentiation of the tumor cells described as G1 or G2 on the basis of the proliferation index Ki-67 (MIB1 antibody), is the strongest prognostic factor in patients with gastro-entero--pancreatic NET (GEP-NET). Data from various studies indicate that in patients with NET G1 and low G2 (Ki-67 from 3 to 10%), significantly better results of treatment are obtained in the form of an increased median PFS and OS in comparison with patients with NET G2 with higher Ki-67 ≥ 10% and on NET G3 with Ki-67 > 20%. This is one of the main factors affecting international recommendations concerning the treatment of neuroendocrine tumors, for example, of the European Association of Nuclear Medicine (EANM), European Neuroendocrine Tumor Society (ENETS), or North American Neuroendocrine Tumors Society (NANETS) [1, 7, 17, 18].

Even though the Ki-67 index is most commonly used for NEN classification, it is burdened by a sampling error as there are differences in Ki-67 within the whole tumor and/or its metastases. The next factor affecting the effectiveness of treatment is the localization of the primary GEP-NET lesion. Radiological responses to treatment, according to the classification of Response Evaluation Criteria in Solid Tumors (RECIST) are more frequent in the case of pancreatic NET in comparison with other localizations, but with a shorter time of duration. The disease recurrence is also faster in patients with hormonally active, symptomatic NET in comparison with NET without secretory activity [5, 6, 9–11, 14, 17–19].

The results of some studies indicate that the degree of liver burden by the tumor and the patient's performance status (PS), according to WHO (World Health Organization) or ECOG (Eastern Cooperative Oncology Group), and rapid clinical improvement directly after treatment are independent prognostic factors of overall survival (OS) and predictive ones for the effectiveness of RLT (PRRT) [2, 6, 9–11].

SSTR-2 overexpression (based on the intensity of radiopharmaceutical accumulation 3 and 4 according to Krenning's qualitative scale) appears to be directly associated with the RLT result. Radiopharmaceuticals attaching with high specificity to an appropriate transmembrane receptor may be used when there are specific clinical, radiological, or molecular indicators that justify their use. Up to now, the Krenning scale is used as a reference point in selecting patients for PRRT [1, 17, 18].

Natural development of the NET and gradual dedifferentiation of tumor cells with the acquisition of loss of overexpression of the receptor subtype SST 2 and the further heterogeneity and variability of receptors on tumor cells, which leads to the concept of "target heterogeneity", is increasingly emphasized. This molecular development of tumor cells affects not only therapeutic decisions, but also the results of target therapy [20]. As tumors distinguish, different cell populations appear in them with the expression of other receptor systems and overexpression of the glucose transporter receptor (GLUT). A positive result of FDG PET (fluoro--deoxyglucose positron emission tomography) in well--differentiated NET of an intermediate or high grade identifies the heterogeneous components of the disease and additionally is a poor prognostic and predictive factor of the response to RLT [7, 14, 21]. The NET-PET scale proposed by Chan et al. [22] has made the NET FDG- and ^{68}Ga-PET-positive characterization objective, but it is still missing prospective validation, especially from the point of view of prognostic value. Metabolic parameters, such as the standard uptake value SUV_{max} or SUV_{mean}, the metabolic tumor volume (MTV), and total lesion glycolysis (TLG) did not provide any coherent results from the point of view of predictive factors [23].

A significant group of patients with neuroendocrine tumors do not respond to treatment despite the high expression of SSTR, low Ki-67, low burden of tumor lesions to the liver, and lack of FDG uptake in PET analysis. Graf et al. [24] proposed that among all known significant clinical and pathological parameters the "quality" of SSTR expression, evaluated visually in SRI analysis (imaging of somatostatin receptors) on the basis of MIP images (maximal intensity of projection), should be the criterion for qualifying patients for RLT treatment. However, this proposal still does not take into consideration the differentiated expression of SSTR in the tumors [1, 6, 7, 9, 11, 22–24]. The short range of lutetium-177 (^{177}Lu) irradiation may lead to the lack of irradiation of a tumor with a large volume and low or heterogeneous SSTR expression. Data encompassing patients with a disease with heterogeneous SST receptor activity indicate that the 28-month median PFS for NET G1 and NET G2 was shorter than for patients with homogeneous SSTR expression. The "quality" of SSTR expression has, thus, provided another independent parameter allowing us to foresee the response to PRRT [24].

The effect of the tumor microenvironment on the effectiveness of therapy should also be stressed. Tumor cells change their reactions to drugs through interactions with their environment. The role of the tumor microenvironment (TME) in tumor progression and the effectiveness of various drugs has recently attracted a lot of attention. The tumor microenviron-

ment is the earliest determinant of ligand binding and if many factors in the TME, such as the immunological response, hypoxia factors, etc. do not favor the activity of the receptor-radioligand complex, further action is difficult, which affects the therapeutic efficacy. When TME is favorable, the further course of radioligand action is determined by physical and chemical factors such as the biological $T_{1/2}$ and the receptor density. This is a dynamic process in time that explains the phenomenon of the differentiated response to RLT despite the currently used criteria and guidelines based on the appropriate selection of patients. Besides the above-mentioned factors, the effectiveness and toxicity of radioligands are also time dependent. The response to RLT, in general, does not depend on the dose, is non-linear, and delayed, especially in midgut type tumors, and sometimes the objective response to treatment can only be seen a year or even 2 years after the last cycle of radioligand treatment. During successive cycles of treatment, genetic changes, and selection of dedifferentiated clones of tumor cells affect the degree of expression of selected molecular targets, which is directly translated to the effectiveness of therapy [25].

Theranostics is the concept of selecting patients for targeted RLT based on the imaging phenotype in the generally concomitant functional diagnostic analysis. However, the appearance of heterogeneity in receptor expression in different stages of tumor progression is an inevitable challenge for the future [23–26].

RLT/PRRT effectiveness

During the last two decades, RLT/PRRT using ^{90}Y and ^{177}Lu DOTA SSTA has proved to be an effective therapy for patients with advanced, unresectable, and progressing NEN in respect to radiological and marker responses, in mitigation of clinical symptoms, and improvement of the quality of life evaluated by standard questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC QLQ C-30 and GI NET21) [10–12, 15].

Currently, most clinical trials concerning RLT/PRRT focus on ^{177}Lu [DOTA0.Tyr3] (DOTATATE). The radiopharmaceutical is composed of the radioisotope lutetium-177, which is a medium-energetic β-emitter with the maximum energy of 0.5 MeV and maximum tissue penetration of 1–2 mm. Its half-life is 6.7 days. ^{177}Lu also emits low energy radiation with an energy of 208 and 113 keV making up 10% and 6% of the emitted radiation, which makes possible scintigraphic imaging and calculating precise internal dosimetry using the same therapeutic compound [1, 6–9, 12, 14, 15].

The capture of radioactivity, expressed as the percentage of administered ^{177}Lu-DOTATATE activity was comparable with the use of ^{177}Lu DOTATOC in organs such as the kidneys, spleen, and liver, but was three to four times higher in 4 out of 5 tumor lesions [13]. Therefore, ^{177}Lu-DOTATATE has a potential advantage due to higher absorbed doses, which may be attained in most neoplasms without increasing the accumulated doses in critical organs, which could potentially limit the therapy [13, 26, 27].

The first elaboration about the use of ^{177}Lu DOTATATE was published by Kwekkeboom et al. [28] in 2003. The trial encompassed 35 patients with GEP-NETs. In the patients, dose acceleration was used from 3.7 GBq, 5.55 GBq to 7.4 GBq, ^{177}Lu DOTATATE to the final cumulative dose of 22.2–29.6 GBq, obtaining partial and complete responses in 38% (according to WHO response criteria). No serious adverse effects were observed in the studied group [28]. In the next study, the same group of scientists analyzed the response to ^{177}Lu-DO- TATATE depending on the type of tumor in 310 patients [6]. Patients were treated up to planned cumulative activity 22.2–29.6 GBq. The general objective response rate (ORR) was 46%. The result of this study indicated a significant effect of PRRT on survival with a median OS of over 48 months and median PFS of 33 months [6]. Direct comparison with data from the literature concerning similar groups of patients indicated a significant 40–72-month benefit for survival in persons treated with PRRT [29].

The results of the next prospective phase I/II trial encompassing 51 patients with advanced unresectable mainly GEP-NET were published by Bodei et al. [9]. The aim was to evaluate the effectiveness and toxicity of therapy using ^{177}Lu-DOTATATE. Patients were divided into 2 groups, receiving escalated activities from 3.7 to 5.18 GBq and from 5.18 to 7.4 GBq, with cumulated activity up to 29 GBq, based on dosimetry. Partial (PR) and complete (CRO) responses were observed in 15 patients (32.6%). Median PFS was 36 months, and the percentage of 36-month overall survival — 68%. Patients who did not respond to treatment and patients with the massive occupation of the liver had poorer survival rates [9].

Even though the data do not come from solid, prospective phase-III trials, this significant difference in survival with a high probability reflects the true effect of RLT/PRRT as a very effective therapeutic method in advanced unresectable NET [2, 6, 28, 29]. A significant breakthrough in using RLT were the results of the NETTER-1 study with randomization ^{177}Lu- DOTATATE *vs.* Octreotide LAR in large doses of 60 mg i.m. given every 28 days to patients with unresectable progressing neuroendocrine tumors derived from the midgut after progression on SSA analogs [15].

In this phase-III trial, the effectiveness and safety of using ^{177}Lu- DOTATATE was evaluated in 229 pa-

tients with advanced well-differentiated G1 and G2, progressing neuroendocrine tumors derived from the midgut after progression on SSA analogs (Somatostatin Analogs). Altogether 111 patients received ^{177}Lu- DOTATATE in a dose of 7.4 GBq administered every 8 weeks in the form of four intravenous infusions with the continuation of treatment with SSA analogs (octreotide LAR 30 mg given intramuscularly between administration of PRRT). On the other hand, the control group of 110 patients received 60 mg octreotide LAR intramuscularly every 4 weeks (dose not compliant with registration indications). The primary endpoint was PFS, and the secondary endpoints were ORR, OS, safety, and the profile of adverse effects. The results indicated a significantly higher — 20-month PPS index of 65.2% (95% CI, 50.0–76.8) in the group receiving ^{177}Lu--DOTATATE in comparison with 10.8% (95% CI, 3.5–23.0) in the control group. In this trial, ORR was found to be 18% in the group receiving ^{177}Lu--DOTATATE in comparison with 3% in the control group ($p < 0.001$). These data translated to the significant lengthening of median PFS in the group treated with ^{177}Lu-DOTATATE — 28.4 months compared to 8.5 months in the group receiving octreotide LAR. The hazard ratio was 0.21 (95% CI 0.14–0.33), which was associated with a 79 percent reduction of the relative risk of progression in the group treated with radioisotope therapy. Moreover, permanent therapeutic benefits associated with ^{177}Lu-DOTATATE administration were observed regardless of stratification and prognostic factors, including the following: level of radiopharmaceutical uptake in scintigraphy, tumor grade, age, sex, and concentration of tumor markers. The most common adverse effects in patients treated with ^{177}Lu-DOTATATE were nausea (59%) and vomiting (47%), which, in over 65% of cases, were ascribed to the amino acids given before treatment. The frequency of grade 3 or 4 adverse effects was similar in both groups; however, hematological events occurred only in the PRRT treated group. Lymphopenia, thrombocytopenia, and anemia at grade 3/4 occurred in 9%, 2%, and 1% patients, respectively. Two patients treated with ^{177}Lu-DOTATATE (1.8%) developed MDS, but there was no evidence of kidney toxicity in the observed period (the median time of observation was 14 months) [15].

In the first update of data from 2018 concerning OS and PFS in the population of the NETTER-1 trial, median OS in the arm with octreotide 60 mg *i.m.* every 28 days was 27.4 months, whereas in the arm with ^{177}Lu-DOTATATE, it had still not been reached. The hazard ratio (HR) for PFS was unchanged in relation to the HR presented in the original publication [30].

The final results of the NETTER-1 trial were presented at the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) in 2021 and were published in November in *Lancet Oncology*. The median observation time was over 6.3 years. The final OS analysis (secondary endpoint) in the ITT (intention to treat) population did not attain statistical significance between the tested group (RLT/PRRT) and the control group (Octreotide 60 mg) HR = 0.84; 95% CI 0.60–1.17. This finding could have been affected by the high percentage (36%) of patients in the control arm who received RLT/PRRT after progression (crossover). Median OS was 48 months in the study arm and 36.3 months in the control arm. Annual indices of overall survival up to 5 years in group receiving ^{177}Lu-DOTATATE in comparison with the control group were: 1 year, 91.0% (95% CI 84.0–95.1) *vs.* 79.7%(70.8–86.1); 2 years, 76.0% (66.7–83.0) compared with 62.7% (52.6–71.2); 3 years, 61.4% (51.4–69.9) *vs.* 50.1% (40.0–59.4); 4 years, 49.5% (39.5–58.6) *vs.* 41.8% (31.8–51.4); 5years, 37.1% (27.8–46.4) compared with 35.4% (25–7–45–2). In two patients treated with ^{177}Lu-DOTATATE (1.8%), MDS developed, which is in agreement with earlier reports. During long-term observation, no new MDS or ALL cases were observed. No new signals concerning safety appeared during long--term observation [16].

The analysis of the quality of life in the NETTER-1 trial was published separately. QOL (quality of life) results were evaluated by QLQ C-30 and G.I. NET-21 questionnaires. The patients filled in the questionnaires at the beginning of the trial and then every 12 weeks until disease progression. The primary endpoint was time-to-QOL deterioration (TTD) which was counted if the QOL of the patient decreased by ≥ 10 points. The QOL result was significantly better in the arm with ^{177}Lu-DOTATATE compared with patients in the arm with octreotide, who were given high doses, in respect to the general state of health (HR= 0.41; $p < 0.001$), physical functioning (HR = 0.52; $p < 0.015$), diarrhea (HR = 0.47; $p = 0.011$), and fatigue (HR = 0.62; $p = 0.03$). The ^{177}Lu-DOTATATE arm did not yield poorer results for any of the parameters [31].

Moreover, in the publication by Strosberg in the *Journal of Nuclear Medicine* in March 2021, an analysis of the diaries of symptoms of patients from the NETTER-1 trial was presented. These data indicate that besides improvement of PFS and prolonging TTD in respect to the quality of life, ^{177}LuDOTATATE treatment is also associated with a statistically significant alleviation of the symptoms, which gives the patients measurable benefits compared with octreotide LAR in the nonstandard dose of 60 mg *i.m.* [32]. A significant decrease was observed in the number of days when patients suffered from stomach pain, diarrhea, and facial flushing associated with carcinoid symptoms. The alleviation of these typical symptoms is particularly important for patients with progressing midgut NET and reflects

the general benefit of using ^{177}Lu-DOTATATE in this population of patients [32].

During the ESMO 2019 Congress, results were presented of the analysis of the correlation between an objective radiological response and PFS, evaluating the dependence between the dynamics of the size of "targeted" lesions and the effectiveness of treatment evaluated as an increase in median PFS in patients treated in the NETTER-1 trial. In the case of patients treated with nonstandard doses of octreotide 60 mg, based on the analysis of Cox regression, a 9-percent reduction in the risk of progression was obtained for each increase of the fraction with a decrease in the size of the lesion — HR = 0.914; 95% CI 0.86–0.97; p = 0.0034. Among patients treated with ^{177}Lu DOTATATE no association was shown between the decrease in the size of the lesions and prolongation of median PFS, HR = 1.01; 95% CI 0.98–1.03; p = 0.624, suggesting that therapy with ^{177}Lu-DOTATATE affects PFS prolongation even when no radiological response is observed during treatment [33]. This analysis provides key information on the evaluation of the effectiveness of PRRT treatment, which should not be exclusively based on the percentage of radiological responses based on the RECIST classification.

It is worth noting that despite the recommendation concerning the use of RLT/PRRT in neuroendocrine tumors of the GI tract, no prospective phase-III clinical trials have been performed concerning the use of RLT/PRRT in neuroendocrine tumors derived from the pancreas (panNET). Moreover, the NETTER-1 trial (the largest trial using RLT/PRRT) did not encompass patients with panNET. There are, however, data, both prospective and retrospective, indicating the justification for using RLT/PRRT in panNET. The joint analysis of these trials indicated a median for disease control of 83% (range from 50% to 94%), and median ORR — 58% (13–73%). Median PFS was 25–34 months, and median OS was 42–71 months [6, 29, 34–37].

During the ASCO 2021 Congress, data were presented from a retrospective registry of patients with unresectable or metastatic well-differentiated, SSTR-positive, progressing neuroendocrine tumors of the pancreas panNET, treated with ^{177}Lu-DOTATATE in Great Britain, France, and Spain (NETTER-R). The analysis encompassed patients, who received ≥ 1 administration of ^{177}Lu-DOTATATE. The primary endpoint was PFS. Secondary endpoints included OS, safety, and response to treatment. This registry included data from 110 patients. The effectiveness of therapy was evaluated in 63 patients according to RECIST v1.1 criteria. Median PFS was 24.8 months (95% CI 17.5–34.5), and ORR — 40.3% (95% CI 28.1–53.6); all responses were partial. The index of response, including radiological, clinical, metabolic, and marker evaluation, which could be estimated in 100 patients, was 54.0% (95% CI 43.7–64.0), including 2 patients with CR (Complet Response). During the time of observation, whose median was 24.5 months (2.0–123.4), median OS attained was 41.4 months (95% CI 28.6–50.2). In 71.8% (n = 79/110) patients at least one treatment-emergent adverse event (TEAE) occurred. The most common ones were nausea (28.2%) and fatigue (22.7%). Anemia and grade 3 lymphopenia occurred in 1 (0.9%) and 4 (3.6%) patients, respectively. Treatment-related adverse effects concerning the kidneys occurred in 6 patients (5.5%; grade 1: n = 1, grade 2: n = 2, grade 3: n = 3). During the period of observation, no ALL nor MDS were observed.

The presented data concerning everyday clinical practice led to the conclusion that therapy with ^{177}Lu-DOTATATE for pan-NET is well tolerated, and the safety profile s in agreement with the results of NETTER-1. In the limited time of observation, OS and PFS were favorable compared with cohorts of patients with panNET progression treated with other systemic drugs [38].

RLT/PRRT in NET G3

With the new classification of neuroendocrine tumors from 2017 and 2019, particular attention was paid to the possibility of utilizing RLT in patients with NET G3 tumors, in whom in 60–70% of cases the primary lesion is in the pancreas. The biology of this group of tumors is not completely understood, and effective therapies are being sought.

The published data concerning RLT in NET G3 in a group of about 280 patients in four retrospective trials with the number of patients in the range of 28–149 with Ki-67 >20% indicate that PRRT should also be considered for this indication [40–43]. General results have shown indices of disease control in the range 30–80%, PFS 9–23 months, and OS 19–53 months. The results were significantly better in patients with Ki-67 < 55% compared with patients with higher Ki-67 values [9, 41–43]. RLT can be considered in patients with NET G3, but careful selection of patients is necessary, and further prospective studies are required to further determine prognostic and predictive factors in this group of patients. The NETTER-2 trial including patients with NET derived from the pancreas has started recently aiming to solve this problem (NCT03972488).

Combined RLT + chemotherapy treatment

According to the newest tendencies in oncology, experiments using RLT/PRRT are concentrated on combined therapies which allow more effective treatment of patients with NEN with SSA receptor overex-

pression. Moreover, multimodal therapies frequently are characterized by a balanced toxicity profile. So far, few studies have been performed evaluating the effect of therapies combined with PRRT. Chemotherapy in low doses may have a radiosensitizing effect by increasing DNA lesions, inhibiting DNA repair, stopping the proliferation of cells, reoxygenation of tumor cells, synchronization of the cell cycle, or apoptosis. The most frequently used substances in treatment combined with PRRT are capecitabine, temozolomide, and 5-fluorouracil (5-FU) [43].

The first report on combined treatment was from Rotterdam, where radiosensitizing capecitabine was used with ^{177}Lu-DOTATATE. In this study, the safety of four cycles of PPRT [7.4 GBq (^{177}Lu) Lu-Octreotate] combined with capecitabine (1650 mg/m^2 daily for 2 weeks) was evaluated. Among seven patients included in the study, one grade 3 anemia and one grade 3 thrombocytopenia were observed. No other serious adverse effects were observed [44].

A phase-II trial using combined chemotherapy and PRRT was conducted by an Australian group. In the preliminary study ^{177}Lu DOTATATE (7.8 GBq in each cycle) was used with capecitabine in the case of progressing, disseminated NEN. Encouraging results were obtained in respect to treatment response: 24% objective responses, 70% stable disease (SD), and in only 6% progressive disease (PD) was observed. Median PFS and median OS were not attained with the median observation of 16 months (range 5–33 months). Survival after 1 year and 2 years was 91% (95% CI 75–98%) and 88% (95% CI 71–96%) respectively [45]

The next study by the same group yielded even better results using a combination of standard activity and a protocol encompassing, on the average, four administrations of ^{177}Lu DOTATATE (7.8 GBq in each cycle) and chemotherapy with capecitabine and temozolomide in treating advanced NET. In about 3% of patients, grade 3 nausea occurred, and in about 6% grade 3 neutropenia. About 53–70% of patients had ORR to the treatment. The percentage of CR was relatively high at 13–15% [46]. Patients attained a median PFS of 48 months, and median OS after median observation of 33 months was not reached [46]. It is worth pointing out that the response indices were higher in patients with gastric-pancreatic NET than in patients with primary enteric-NETs; CR 18% *vs.* 13%, PR 64% *vs.* 13%, SD 12% *vs.* 67% [46].

In a similar study, Nicolini et al. [47] with combined therapy PRRT plus capecitabine in 37 selected patients with SSR-positive and FDG-positive GEP-NET and (Ki-67% < 55%), median PFS was 31 months, and median OS after median observation of 38 months was not reached. The most common symptoms of toxicity G3/G4 were neutropenia (11%), fatigue (5%), and diarrhea (5%). According to RECIST 1.1, a response was obtained in 30% of patients, and stabilization in 55%.

Pioneering work from Poland using combined therapy for patients with advanced forms of GEP-NET was presented by Kolasińska-Ćwikła et al. [48] at the European Neuroendocrine Tumor Society (ENETS) Congress in 2021. In a single-arm intervention trial of combined PRRT + CAPTEM treatment, 21 patients were included (NCT04194125). In 14 patients (67%) PR was attained, and the rest (33%) had SD. Control of the disease during the clinical observation was found in 16 (76%) patients. Objective responses were noted in 12 (86%) patients with panNET, the range of the best response in reducing target lesions was 32–88%, and in the remaining 2 patients SD was observed. In 4 patients who attained PR (RECIST) surgical excision of the primary tumor was performed. During the observation, disease progression occurred in 4 persons, whereas in the remaining patients PR or SD was maintained [48]. This treatment caused a low percentage of serious adverse grade 3 and 4 effects. During therapy, transitional lymphopenia occurred in most patients which normalized during the clinical observation [49]. In the recent update of PFS of this trail indicated that median PFS for all subjects including (95%CI) was 32.0 months (23.0–n.r.), for subjects with pancreatic NET 28.0 months (26.0–n.r.), and those with midgut = 32.0 months (19.0–n.r.) [50].

Conclusions

Radioligand therapy (RLT), previous PRRT with the use of radioisotope-labeled synthetic somatostatin analogs bring benefits in the reduction of symptoms and potentially prolong overall survival in patients with unresectable, advanced, and progressing GEP-NET. RLT is a reasonable treatment option for patients with neuroendocrine tumors showing overexpression of somatostatin receptors. The NETTER-1 clinical trial, the first phase-III clinical trial in the group of patients with neuroendocrine tumors derived from the midgut after progression on SSA analogs showed that treatment with ^{177}Lu-DOTATATE has significant clinical effects and statistically changes median PFS (HR = 0.18; 95% CI 0.11–0.29; $p < 0.0001$), as well as clinically increases median OS by 11.7 months compared with long-acting high dose octreotide (60 mg i.m.). Data from various treatment centers using RLT/PRRT of patients with neuroendocrine tumors with other localizations of the primary lesion also provide evidence justifying this type of treatment.

Moreover, this treatment is safe with acceptable toxicity and has a favorable effect on the quality of life. Numerous prospective trials are being conducted to show the effectiveness of RLT treatment in patients

with NET with other localizations than the midgut. Prognostic and predictive factors of response to this type of treatment are being sought.

Intensive research is ongoing on combined therapies using RLT and chemotherapy to improve effectiveness. Other variants of treatment using RLT/PRRT are also the subject of interest of researchers, as well as using alpha, instead of beta, radiation to improve RLT effectiveness.

Conflict of interest

AAA travel grant 2020. AAA advisory board in 2021.

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VIA MEDICA

CASE REPORT

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Long-term overall survival in a patient with non-small cell lung cancer with *KRAS* mutation

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ABSTRACT

The prognosis of patients with metastatic non-small cell lung cancer depends not only on the general condition and stage of the disease but also on the treatment method. Management of lung cancer in stage 4, usually requires a multidisciplinary approach. Frequently in the treatment process, we combine local and systemic treatment. By detecting new therapeutic targets, we can incorporate new elements of therapy. In the described case, the treatment sequence: chemotherapy, immunotherapy, targeted treatment combined with symptomatic local treatment resulted in prolonged survival time and maintaining a good quality of life. The new molecule sotorasib is a drug targeting the G12C mutation in the Kirsten rat sarcoma virus (KRAS) gene approved by the FDA and EMA.
Key words: non-small-cell lung cancer, *KRAS* mutation, sotorasib

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Case report

A 62-year-old male patient with a history of long-term smoking (a pack a day for 25 years, had not smoked for 10 years) was referred for treatment and further diagnostics due to increasing exercise dyspnea. The patient had symptoms of progressive superior vena cava syndrome. Chest X-ray showed a tumor at the apex of the right lung (Fig. 1). Computed tomography confirmed pressure on the mediastinal structures, including the superior vein. To reduce the symptoms, before the diagnosis, the patient was secured by implanting a stent into the narrowed superior vein (Fig. 2). His symptoms decreased. Urgent diagnosis of the neoplastic lesion was performed. In January 2019, adenocarcinoma was diagnosed by bronchoscopy with ultrasound (EBUS). Molecular tests performed at this stage did not reveal any driver mutations that would allow targeted treatment. Genetic alterations in the EGFR,

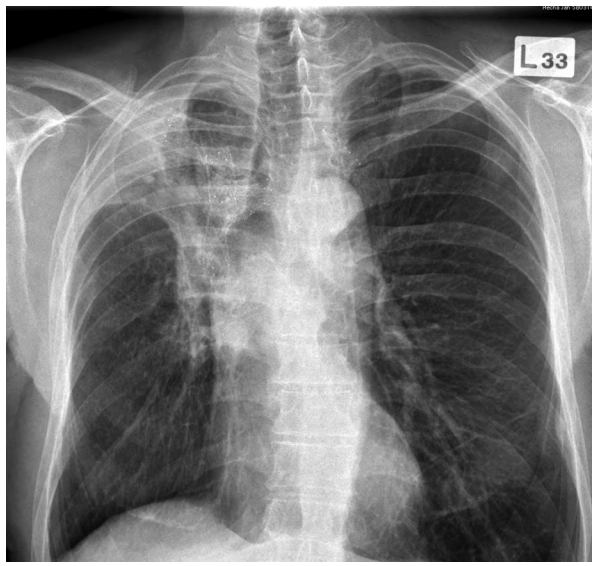

Figure 1. Tumor at the apex of the right lung (chest X-ray)

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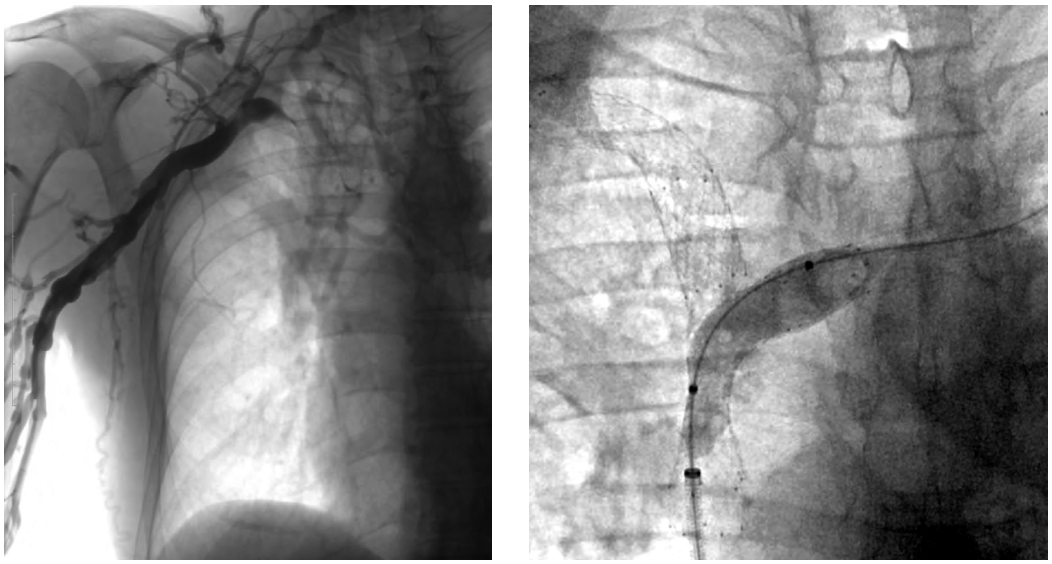

Figure 2. Effective treatment of symptoms by implanting a stent into the narrowed superior vein

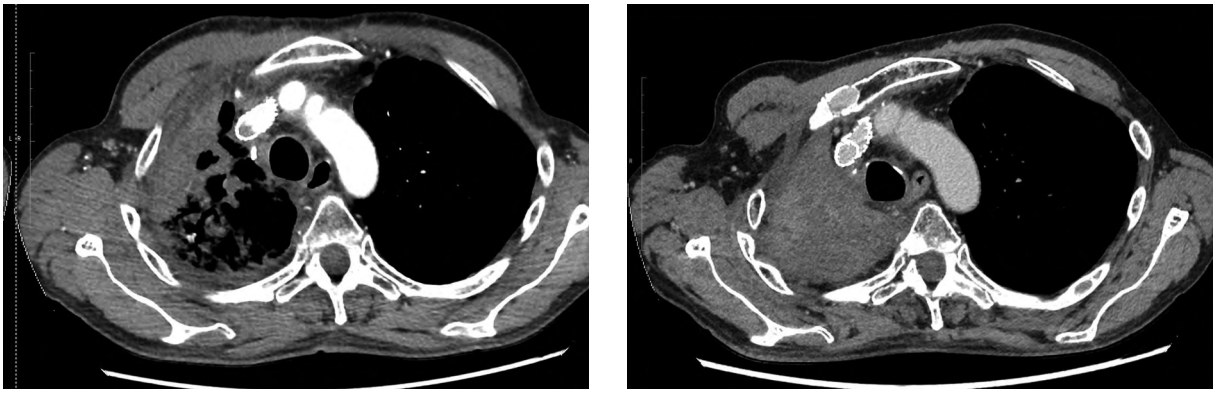

Figure 3. Progression in the lungs after 10 months of treatment with atezolizumab

ALK, ROS-1 genes were excluded. Expression of PD-L1 (programmed death protein ligand-1) was present on 10% of the tumor cells. In 2019, it was not possible to include the patient in the treatment combined with pembrolizumab due to the lack of reimbursement. The patient received chemotherapy in the cisplatin + pemetrexed regimen. After two cycles, a good response to treatment was obtained. Unfortunately, in the evaluation after 4 cycles, there was a progression of tumor in the chest. Additionally, the patient reported double vision. Magnetic resonance imaging (MRI) revealed a pathological mass in the right eye socket. The patient was scheduled for radiotherapy (30 Gy) of the lesion in the eyeball. After radiotherapy, in September 2019, the second line of systemic treatment was started. The patient received immunotherapy. After 10 months of successful treatment with atezolizumab, a progression was observed in the lungs (Fig. 3) and the central nervous system (Fig. 4). Based on recent reports, the patient was ordered a G12C mutation test in the KRAS gene. After obtaining a positive result, the treatment with sotorasib was started, and the disease stabilized. The patient received treatment for over a year with very good tolerance. Optimal sequential treatment, including molecularly targeted therapy and symptomatic local therapy, allowed the patient to achieve long-term survival (Fig. 5).

Discussion

The US Food and Drug Administration granted accelerated approval to sotorasib for treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a G12C mutation in the KRAS gene who have received at least one prior systemic

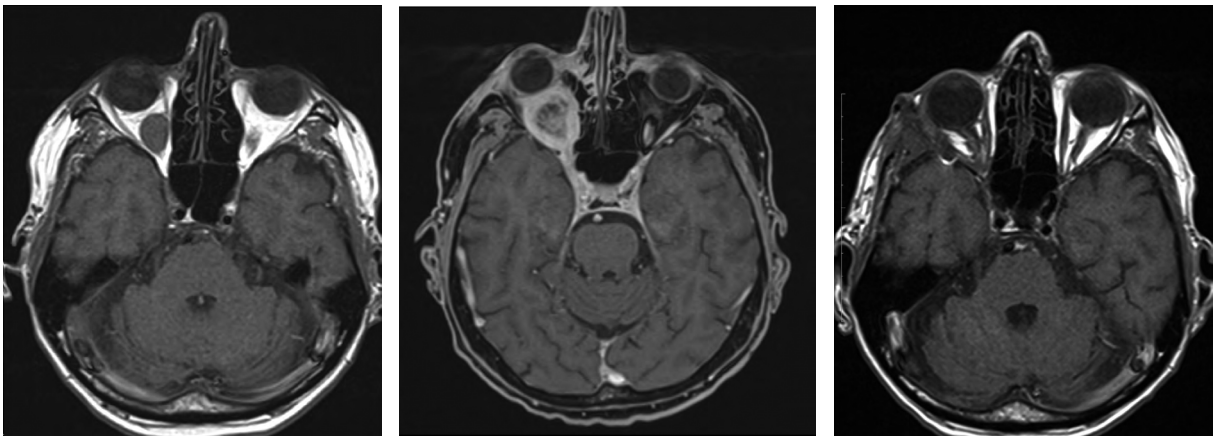

Figure 4. Metastatic lesion in the eye socket after surgery, radiotherapy and completion of immunotherapy

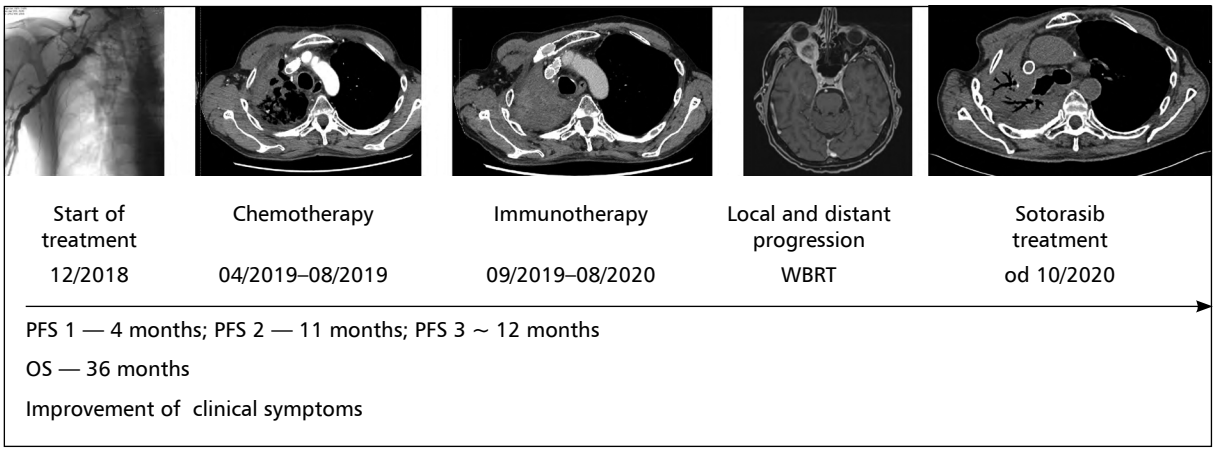

Figure 5. Summary of treatment; WBRT — whole brain radiotherapy; PFS — progression-free survival; OS — overall survival

therapy. The registration was based on the results of the CodeBreaK 100 multi-center, single-arm, open-label clinical study (NCT03600883), which enrolled patients with locally advanced or metastatic NSCLC with the G12C mutation in the KRAS gene. The drug effectiveness was assessed in 124 patients whose disease had progressed after at least one prior systemic therapy. Patients received sotorasib 960 mg daily orally until disease progression or unacceptable toxicity. The main efficacy endpoints were objective response rate (ORR) according to RECIST 1.1 and duration of response (DOR). The ORR was 36% (95% CI: 28%, 45%) with a median duration of response of 10 months. The most common adverse reactions (≥ 20%) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. Laboratory abnormalities, such as decreased lymphocyte counts, decreased hemoglobin levels, and increased liver enzymes, were also observed. The recommended dose of sotorasib is 960 mg orally once daily with or without food. It is the first registered targeted therapy in the indication of patients with solid tumors with a mutation in the KRAS gene [1].

KRAS mutations occur in 20–30% of adenocarcinoma patients, especially tobacco users (5% of non-smoking patients may also have KRAS mutations). These mutations are more common in males and Caucasian patients rather than females and Asians. Since mutations in the KRAS gene exclude the presence of other genetic abnormalities, the examination of the KRAS gene may have some value in qualifying for other genetic tests [2]. Sotorasib is the first drug conditionally approved in the European Union for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy. Adagrasib and combinations of these drugs including immunotherapy, are also available in clinical

trials. It is also being assessed whether drugs targeting the G12C mutation in the KRAS gene will be effective in the first-line setting [3].

Conflict of interest

Author declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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A case of pathologic complete response after neoadjuvant triplet chemotherapy for locally advanced colon cancer with mismatch repair enzyme proficiency

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ABSTRACT

Patients with potentially resectable colon cancer and expected to have negative margins should undergo resection rather than neoadjuvant chemotherapy. Recent studies have suggested that neoadjuvant immunotherapy may be an option for tumors with mismatch repair enzyme deficiency (dMMR), but standard treatment for locally advanced colon cancer with mismatch repair enzyme proficiency (pMMR) is still unclear. A 37-year-old male patient was diagnosed with clinical stage IIIC (T4b N1a M0) transverse colon cancer. Mismatch repair proteins were proficient. After 3 cycles of oxaliplatin (85 mg/m^2, day 1), irinotecan (150 mg/m^2, IV, day 1), leucovorin (200 mg/m^2, IV, day 1), and 5-fluorouracil (3000 mg/m^2, 46 hours of continuous infusion initiating from day 1), there was a remarkable reduction in the tumoral mass on the abdominal computed tomography. A right hemicolectomy was performed. A pathologic complete response was obtained. Although there is no consensus on which patients are suitable for neoadjuvant therapy in pMMR locally advanced colon cancer, triplet chemotherapy may be a reasonable option in selected patients.

Key words: complete response, colon cancer, neoadjuvant, triplet chemotherapy

Oncol Clin Pract 2023; 19, 2: 114–117

Introduction

Locally advanced colon cancer is defined as the adhesion or invasion of the primary tumor into adjacent structures and organs [1]. Patients with potentially resectable colon cancer and expected to have negative margins should undergo resection rather than neoadjuvant chemotherapy [2]. Neoadjuvant therapy for patients with locally advanced colon cancer is associated with some theoretical advantages, such as administering early effective systemic therapy that might reduce micrometastases, improving compliance with systemic therapy, and downsizing the primary tumor to provide negative surgical margins [3]. However, randomized trials have failed to verify the long-term improvement after neoadjuvant chemotherapy compared with surgery [4, 5]. Although small phase II studies have demonstrated the safety of neoadjuvant chemotherapy [6], few retrospective studies have demonstrated a survival benefit [7, 8]. Mismatch repair enzyme deficient (dMMR) colorectal cancer is responsive to programmed death-1 inhibitors in the metastatic setting. In a recent study, a pathologic complete response rate of 67% and a major pathologic response rate of 95% were ob-

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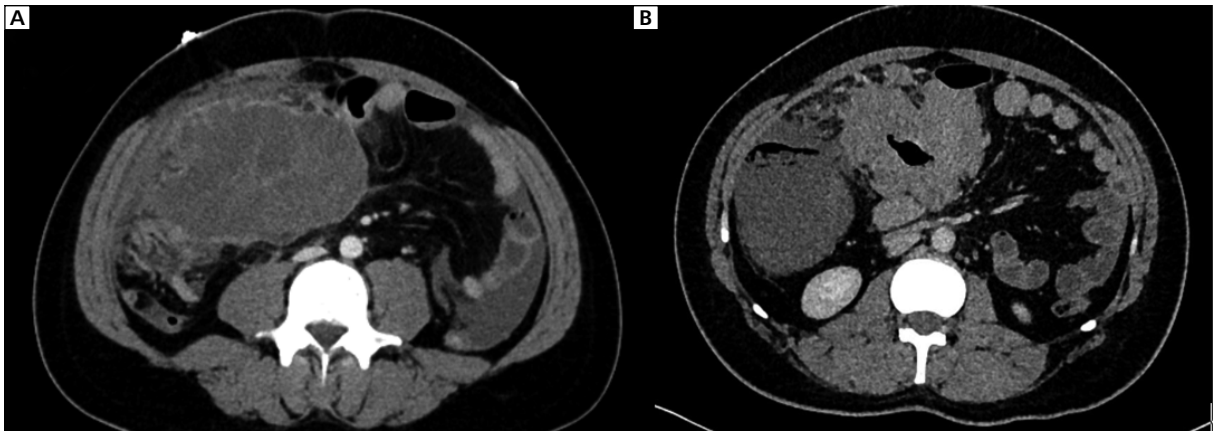

Figure 1. A, B. Malign wall thickening of the hepatic flexure and associated mass beyond the wall extending to the mesentery

tained with short-term neoadjuvant combined immunotherapy in patients with dMMR locally advanced colon cancer [9]. In another recent study, a complete response was achieved in all enrolled patients with dostarlimab in locally advanced rectal cancer with dMMR [10]. The proficient MMR (pMMR) rate is approximately 85 percent in patients with colon cancer.

Although neoadjuvant chemotherapy is not standard in locally advanced colon cancer, it could improve oncological outcomes. However, the efficacy of triplet chemotherapy is still unknown in the neoadjuvant setting in pMMR patients. We aimed to present a case with a complete pathologic response to neoadjuvant chemotherapy with mFOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) for transverse colon cancer.

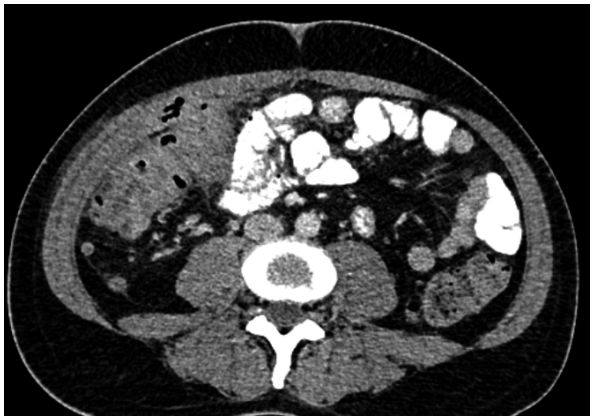

Figure 2. Abdominal tomography image after 3 cycles of triplet chemotherapy

Case presentation

A 37-year-old male patient presented with abdominal pain and fatigue. Physical examination revealed tenderness in the epigastric region and pale conjunctiva. Laboratory data showed iron deficiency anemia [hemoglobin, 9.6 g/dL, mean corpuscular volume 72 (80–100) fl, iron 21 (50–170) μg/dL, total iron binding capacity 314%, transferrin saturation 7% (20–50)]. A fecal occult blood test was positive. Carcinoembryonic antigen was 7 ng/mL. CA19.9 was 17 ng/mL. Colonoscopy showed a fragile tumor mass in the transverse colon that completely occluded the lumen. A biopsy showed colon adenocarcinoma, RAS wild type, and BRAF V600E mutation status was negative. Mismatch repair proteins were proficient. Human epidermal growth factor receptor 2 was negative. Peritoneal acid examination cytology was negative. Abdominal computed tomography (CT) showed a giant 14 × 12 cm mass in the right upper abdomen (Fig. 1). The tumoral mass invaded the third part of the duodenum, was close to the pancreatic uncinate process, invaded the jejunal segments, and surrounded the ileum. It was not occluding the intestines. There was a periportal 8 mm lymph node and a 1 cm lymph node in the meso of the transverse colon. There was no metastasis in the thorax CT. The patient was diagnosed with clinical stage IIIC (T4b N1a M0) transverse colon cancer. He was considered inoperable because of the extensive invasion of surrounding organs and the difficulty of margin-negative surgery. He was started on oxaliplatin (85 mg/m^2, day 1), irinotecan (150 mg/m^2, IV, day 1), leucovorin (200 mg/m^2, IV, day 1), and 5-fluorouracil (3000 mg/m^2, 46 hours of continuous infusion initiating from day 1) (FOLFOXIRI given on days 1 and 15, repeated every 4 weeks). After 3 cycles of chemotherapy, there was a remarkable reduction in the tumoral mass in the abdominal CT (Fig. 2), but also there were signs of closed perforation. A right hemicolectomy and ileotransversostomy were performed. The pathology result showed granuloma-like structures and 15 reactive lymph nodes. A pathologic complete response was obtained. There were no residual or distant metastases

in the postoperative imaging. The patient was administered 3 cycles of the adjuvant FOLFOX (days 1 and 15, every 4 weeks) regimen. The patient was disease-free in the last 20 months of follow-up.

Discussion

In the present case report, a pathologic complete response was achieved for locally advanced colon cancer after only 3 cycles of the neoadjuvant FOLFOXIRI regimen.

The standard treatment in early-stage colon cancer is surgical resection and adjuvant chemotherapy is administered according to the pathological stage. Multivisceral resection is an option for locally advanced and potentially resectable primary colon cancers. However, it has been reported that multivisceral resection might cause a longer hospital stay, delay in the start of systemic chemotherapy, and an increase in the risk of postoperative complications [11]. Neoadjuvant treatment is related to various theoretical advantages such as early administration of effective systemic therapy, downsizing the primary tumor, and improved surgery margins [4]. In 2016, neoadjuvant chemotherapy was offered as a treatment option for patients with bulky nodal disease or clinical T4b colon cancer in the National Comprehensive Cancer Network (NCCN) guidelines [12]. In the present case, a giant tumoral mass invaded the duodenum, ileum, and jejunum and was adjacent to the pancreas on the abdominal CT on admission. After 3 courses of FOLFOXIRI, there was a significant reduction in the tumoral mass, and surgical resection was performed without multivisceral resection.

The benefit of preoperative chemotherapy for patients with primary colon cancer was addressed in the phase III trial FOxTROT (T3-4N0-2, nonobstructed primary colon cancer) [13]. In the FOxTROT study, the pathologic complete response rate was 4% [13]. Preoperative chemotherapy was associated with lower rates of incomplete resection and regression of histologic staging in both the pathologic tumor and nodal stages [13]. In addition, there was a trend towards lower rates of disease recurrence at two years [13]. In studies, pathologic complete response rates of the FOLFOXIRI regimen for neoadjuvant therapy in patients with colorectal cancer ranged from 4.3% to 6.8% [14, 15] In the present case, the FOLFOXIRI regimen was preferred for complete R0 resection in the young and fit patient, and he tolerated the 3 cycles of the triplet regimen well.

The best treatment and follow-up method after neoadjuvant therapy with a pathologic complete response for colon cancer patients remains controversial. In this case, the patient received three cycles of adjuvant FOLFOX, and there was no evidence of metastasis or recurrence. Preliminary studies are showing that neoadjuvant immunotherapy may be the standard of care in patients with locally advanced colon and rectal cancer with dMMR [9, 10]. However, it suggests that neoadjuvant triplet chemotherapy may be the standard of care in patients with locally advanced colon cancer with pMMR and cT4b.

Although there is no consensus on which patients are suitable for neoadjuvant therapy in pMMR locally advanced colon cancer, triplet chemotherapy may be a reasonable option in selected patients.

Authors's contribution

Conception: MZK, MA. Study design: MA, MKE, PFY Data collection: MA, MC, UK. Writing: MZK, PFY, MA. Editing and approval of the final draft: MZK, MA, MC, UK, PFY, MKE, MA.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Challenges in the diagnosis and treatment of peritoneal mesothelioma: a case study and review of the literature

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ABSTRACT

Peritoneal mesothelioma is a rare neoplasm that is associated with multiple diagnostic and therapeutic challenges. Therapeutic guidelines are scarce and based on extrapolative data. Histopathological diagnosis is difficult as neither the morphological finding nor the immunohistochemical stains are specific. The mainstay treatment for resectable disease is cytoreductive surgery with intraperitoneal chemotherapy being a valuable addition. Treatment of non-resectable cases includes platinum-based chemotherapy, immune checkpoint inhibitors, and bevacizumab. We present a case of a 49-year-old woman suffering from inoperable peritoneal mesothelioma, which was initially diagnosed as ovarian cancer and treated accordingly.

Key words: differential diagnosis, ovarian cancer, peritoneal mesothelioma

Oncol Clin Pract 2023; 19, 2: 118–123

Introduction

Mesothelioma is a rare neoplasm associated with a poor prognosis and a high mortality rate. It originates from the serous membranes of the pleura, peritoneum, and pericardium.

The incidence rate in Europe is 0.36 per 100 000 per year. The peritoneum is the second most commonly affected organ, comprising 10–15% of cases [1, 2]. In Poland, 336 cases of mesothelioma were diagnosed in 2019, with an incidence rate of 0.6 cases per 100 000 inhabitants [3, 4]. The incidence is declining worldwide, especially among men. Poland remains one of the countries where the incidence is increasing.

Peritoneal mesothelioma is rare and, therefore, not well investigated. Most of the data are based on studies of more common pleural mesothelioma. The differences and similarities between these two diseases are not well understood. Although asbestos exposure is a significant and predominant risk factor in both conditions, those cancers differ in gene expression and possibly also in molecular pathogenesis [5–7].

The symptoms of peritoneal mesothelioma are largely dependent on the extent of tumor spread in the abdominal cavity and the presence of distant metastases. The most common initial symptom is abdominal distension (30–80% of patients) and abdominal pain (27–58% of patients). Malignant bowel obstruction or perforation can also develop. Frequent symptoms also include poor appetite, early satiety, nausea or vomiting, weight loss, night sweats, fever, new-onset hernia, or urinary complaints. Due to the lack of characteristic symptoms, diagnosis is often delayed. Although symptoms of gastrointestinal involvement are the most common clinical presentation, patients sometimes present with distant metastases to the liver, spleen, thyroid, or brain, or the neoplasm is an incidental diagnosis found at laparoscopy [5, 8].

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Novel immunohistochemical and molecular markers have improved the accuracy of diagnosis. However, in about 14% (high-resource countries) to 50% (developing countries) of mesothelioma, diagnoses are incorrect and result in inadequate treatment and confounding epidemiological studies [6]. We aim to present the case of a patient with primary peritoneal mesothelioma which was misdiagnosed as ovarian cancer.

Case presentation

Clinical history

A 49-year-old woman was referred with a suspicion of ovarian cancer due to abdominal pain, bloating, and ascites. The previous medical history included: obesity, arterial hypertension, and appendectomy. Computed tomography (CT) revealed a solid cystic lesion of the right ovary (32 mm) with accompanying peritoneal implants involving the omentum, liver capsule, and sigmoid, and two lesions (up to 71 mm) in the enlarged spleen. No thoracic lesions were reported. The patient underwent laparotomy with hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and splenectomy. The procedure was performed in a clinical center with extensive experience, but, not in a tertiary center.

Histopathological examination and initial treatment

The histopathological result described numerous foci of adenocarcinoma within both ovaries and the omentum. The involvement of the ovary with small malignant foci and the presence of psammoma bodies resembled a serous papillary adenocarcinoma. Lesions in the omentum were classified as metastases, based on morphology and immunophenotypic examination [CK7 (+), CK20 (–), WT-1 (+)]. The pathological stage was established as pT3cN1. The spleen lesions were found to be vascular malformations. The International Federation of Gynecology and Obstetrics (FIGO) IV ovarian cancer was diagnosed.

The patient underwent six cycles of adjuvant therapy with paclitaxel, carboplatin, and bevacizumab. Post-treatment CT showed stable liver capsule lesions and partial remission in lesions located at the post-splenectomy site. A prominent epigastric hernia was also present in the laparotomy scar. Maintenance bevacizumab had continued but ended prematurely due to the development of a peritoneo-cutaneous fistula.

Further treatment

Three months later, follow-up CT revealed progression of diaphragmatic lesions, pathological common iliac lymph nodes, ascites, consolidations in the left lung and contralateral hydrothorax. The patient was referred to a tertiary center and second-line chemotherapy with carboplatin and gemcitabine was initiated.

A histopathological reevaluation of the initial surgical specimen was ordered. Low-grade serous carcinoma (LGSC) was confirmed with the estrogen receptor (ER) expressed in <1%, progesterone receptor (PR) in < 1%, and Ki67 in 3% of tumor cells. Somatic and germline *BRCA1* and *BRCA2* mutations were excluded by the next-generation sequencing (NGS) test. The concentration of cancer antigen 125 (Ca-125) and human epididymis protein 4 (HE4) was within the normal range. Subsequent CT after 3 months showed stable disease. After further 3 months, CT was stable and both Ca-125 and HE4 levels normalized. After further 4 and 9 months, CT and Ca-125, and HE4 marker levels were stable. Meanwhile, postoperative hernia significantly reduced the patient's quality of life. She was referred for hernia surgery; however, due to the presence of the malignancy, numerous centers refused to operate.

Hernia surgery, clarification of the diagnosis

After confirming the stable disease on positron emission tomography (PET) in combination with a CT scan (PET-CT), a hernia removal was finally performed. The hernial sac contained ingrown intestinal loops and numerous malignant implants. Segmental resection of the ileum was necessary. Histopathological examination revealed neoplastic infiltrations of epithelioid cells with slight atypia, forming solid and papillary structures with metastases to the peri-intestinal lymph nodes. The immunophenotype included calretinin /+/, D2–40 /+/, CK5/6 /+/, and PAX8 /–/. The result contradicted the diagnosis of the ovary as primary cancer and established a new diagnosis of epithelioid mesothelioma. Repeated evaluation of the archival samples yielded results consistent with the new diagnosis. The newly obtained cancer sample expressed ER 3%, with no expression of PR or androgen receptors. Ki-67 was 12.5%. The mitotic index was 2 mitoses per 10 high-power fields. Subsequent CT showed low-grade progression of the peritoneal implants. Metronomic chemotherapy with continuous oral vinorelbine (40 mg 3 times a week) was administered. Treatment did not control the progression; therefore, cisplatin-pemetrexed chemotherapy was initiated. The therapy yielded good disease control. Cisplatin was discontinued after 6 cycles. Since then, the patient has enjoyed good general condition, with improved quality of life after hernia plastic surgery. The maintenance pemetrexed is continued.

Discussion

Peritoneal mesothelioma is a very rare neoplasm with nonspecific symptoms and a poor prognosis [8, 9]. It is likely to be misdiagnosed, especially if it coexists with peritoneal dissemination and other abdominal comorbidities. The literature describes cases of peritoneal mesothelioma resulting in small bowel obstruction [10] or infertility [11]. Other reports call attention to the simultaneous appearance of peritoneal mesothelioma along with endometriosis [12, 13] or breast cancer [14]. In a study of 164 women diagnosed with peritoneal mesothelioma, the mean age of diagnosis was 49 years, and the most frequently reported symptom was abdominal or pelvic pain. Some patients were asymptomatic and had paraneoplastic syndromes or cervical lymphadenopathy. In most cases, a personal or family history of other tumors was present [15].

Few therapeutic guidelines aimed specifically at MPM exist and are largely based on studies of more common pleural mesothelioma [16]. The recommended therapy for resectable disease is typically cytoreductive surgery (CRS). Small studies showed excellent results with hyperthermic intraperitoneal chemotherapy (HIPEC) following CRS [17]. The limitation of HIPEC is patient selection, toxicity, and lack of data from prospective randomized trials [18].

The standard first-line palliative treatment for unresectable disease is based on cisplatin or carboplatin combined with pemetrexed or raltitrexed. The combination of platinum and gemcitabine is considered a valuable alternative [1, 16]. The addition of bevacizumab to the cisplatin-pemetrexed doublet offers a modest survival benefit [19]. The latest National Comprehensive Cancer Network (NCCN) guidelines consider the combination of ipilimumab and nivolumab as another standard first-line therapy in advanced peritoneal mesothelioma. The recommendation is based on a recent phase 3 trial of nivolumab combined with ipilimumab in pleural mesothelioma showing significant improvement in overall survival (OS) compared to standard first-line chemotherapy (median OS — 18.1 *vs.* 14.1 m; HR = 0.74; 96.6% CI 0.60–0.91; p = 0.0020) [20]. Other checkpoint inhibitors were also investigated in mesothelioma. Pembrolizumab demonstrated an objective response rate (ORR) of 20% and a disease control ratio (DCR) of 72%. Atezolizumab combined with bevacizumab showed an ORR of 40% and DCR of 95% in a small study [21].

Vinca alkaloids demonstrated activity in patients with mesothelioma in a single or combined therapy; therefore, they are a reasonable option in subsequent lines [21]. As data on second- or third-line therapy are sparse, it is recommended that patients with peritoneal mesothelioma should be enrolled in clinical trials.

The histopathological diagnosis of peritoneal mesothelioma is challenging and, therefore, prone to diagnostic errors, especially in patients with involved ovaries [5, 6]. Most ovarian tumors are composed of epithelial cells, arranged in solid and tubulopapillary patterns. Low-grade serous carcinoma (LGSC) is characterized by a high architectural variety, including the presence of micropapillae and macropapillae that are usually surrounded by clefts or clear space. Psammoma bodies are a common finding. LGSC cells show mild to moderate nuclear atypia, and the nucleoli are sometimes visible. Mitotic activity is usually less than 2–3 mitotic figures per 10 HPF and necrosis features are seldom seen. The Ki-67 index is relatively low. LGSC cells express epithelial markers, including cytokeratin (AE1/AE3, CAM 5.2) PAX8, WT1, EMA, CA-125, and BER-EP4. The ER expression is high, while PR is approximately 50% positive. Cancer cells exhibit a wild-type p53 pattern. However, there is no diffuse expression of p16 [22–25].

Peritoneal mesotheliomas are made up of cells that are generally similar to mesothelium cells, with an eosinophilic cytoplasm and a cuboidal shape. They usually show mild to moderate nuclear atypia and have noticeable nucleoli; the mitotic figures are usually only slightly visible. About one-third of the cases show the presence of psammoma bodies. The typical patterns of peritoneal mesothelioma are tubular, papillary, and solid. In many cases, they coexist with each other, especially solid and papillary. Unlike LGSC, the papillary pattern is less complex and inconspicuous. In immunohistochemistry, mesothelioma cells are usually positive for CK7, Calretinin, EMA, WT-1, HBME1, CK5/6, and D2–40. What is characteristic of them, however, is the lack of expression of ER, PR, CEA, Leu M1, B72.3, MOC31, claudin-4, and BER-EP4 [22, 23, 26, 27].

The presented case posed many diagnostic challenges which made it difficult to differentiate between these two neoplasms. The examined tumor was composed, among others, of papillary structures with the presence of psammoma bodies, showing features of slight atypia, mitotic index of 2/10 HPF (Fig. 1), and Ki67 that ranged in various measurements from 3 to12.5%. Tumor cells were positive for calretinin, D2-40, and CK5/6. The immunoreactivity for PAX-8 was negative (Fig. 2). This picture could indicate both of the discussed neoplasms.

A common diagnostic problem is a distinction between peritoneal mesothelioma and adenocarcinoma with diffuse peritoneal involvement or primary peritoneal adenocarcinomas, which are morphologically identical to ovarian or fallopian adenocarcinomas. Immunohistochemically, in most cases, MPM shows the expression of calretinin, WT-1, cytokeratin 5/6, and D2–40, while the presence of positive PAX-8 and ER favors the diagnosis of LGSC. High expression of ER and PR is observed in most LGSCs

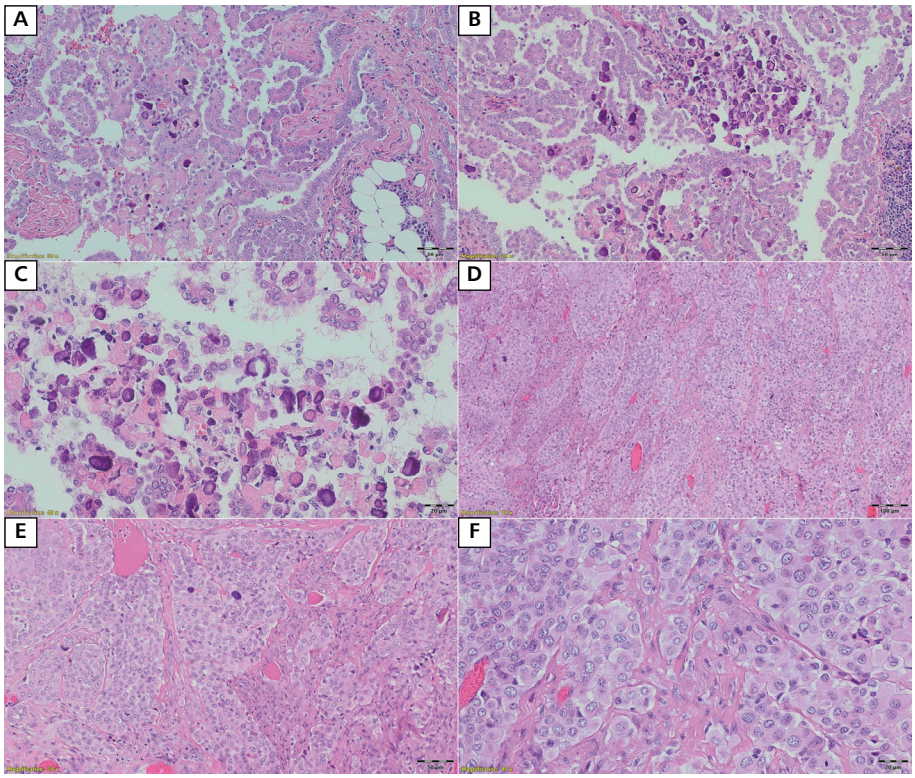

Figure 1. A–C. Papillary pattern of peritoneal mesothelioma with psammoma bodies; **D–F.** Solid pattern of peritoneal mesothelioma. Cells are epithelioid, with eosinophilic cytoplasm and moderate nuclear atypia

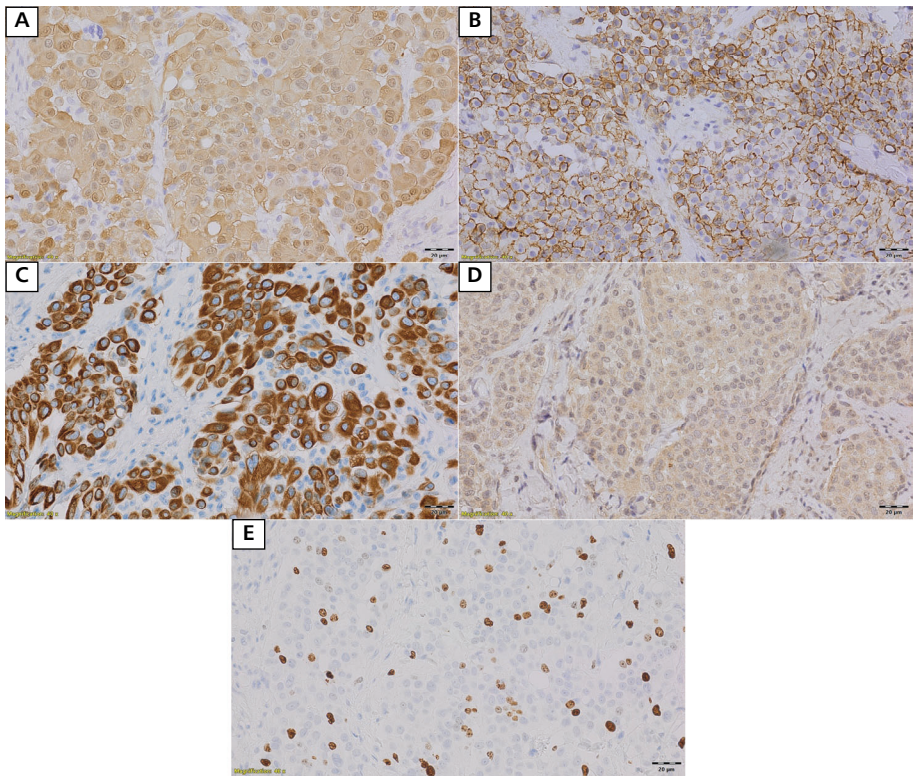

Figure 2. Immunohistochemical examination of peritoneal mesothelioma. Tumor cells are positive for calretinin (**A**), D2–40 (**B**), and CK5/6 (**C**); **D.** The immunoreactivity for PAX-8 was negative; **E.** Ki-67 expression was evaluated as 12.5%

while they are commonly absent in MPMs [22, 23]. Important in understanding the key pathogenetic mechanisms of cancer was the discovery that germline BRCA1-associated protein 1 (BAP1) mutations cause mesothelioma and other cancers (BAP1 cancer syndrome), which distinguishes malignant mesothelioma from benign mesothelial lesions and serous tumors of the ovary [27, 28]. Boussios et al. [29] claim that the PAX-8 gene negativity is a useful diagnostic marker that could be employed for the differential diagnosis of ovarian carcinoma. It was used in the evaluation of the histological preparation of the second surgery in our patient, giving a conclusive diagnosis. However, diagnosis may be hampered by the fact that most patients have an elevated Ca-125 level [30]. It should be noted that CA-125 is produced by mesothelial cells of the pleura and peritoneum, hence its increased level may be present in many diseases related to peritoneal damage, e.g., liver cirrhosis or previous surgery. Although CA-125 is often recognized as a marker of gynecological malignancies, its elevated level may also be present in mesothelioma or even benign conditions such as endometriosis. Therefore, the elevated level of CA-125 should encourage a wide-ranging differential diagnosis [30–35]. Radiological criteria for discrimination of the characteristics of adnexal masses, such as the simple ultrasound rules of the International Ovarian Tumour Analysis (IOTA), should form the basis for the diagnosis of adnexal mass. If the clinical picture is ambiguous, more precise indicators adapted to the clinical situation should be used, such as, e.g., the FDA-approved ROMA and OVA1 algorithms.

Another important aspect in our case described was the use of surgery for the treatment of persistent postoperative epigastric hernia after extensive surgery. It is known to negatively affect quality of life, and this topic is widely described [36]. In the study by Baucom et al. [37], it has been shown that in patients without prior ventral incisional hernia (VIH) who underwent abdominal malignancy resections, the incidence of VIH is high and can impact cancer survival, with pain and the need for additional operation. In the case of our patient, despite the ongoing remission of palliatively treated cancer, many surgical centers refused to remove the hernia. However, recent research shows that VIH repair after abdominal malignancy surgery can improve quality of life, functionality, social function, and satisfaction [38, 39]. More research is needed to assess which patients will benefit most from the procedure, but surgical correction of the treatment complication in cancer patients seems obligatory.

Conclusions

Despite the use of new immunohistochemical and molecular markers, mesothelioma can be misdiagnosed. Therefore, tumors in the abdominal cavity should be carefully evaluated as no single immunohistochemical stain differentiates between LGSC and PMM. In ambiguous cases or treatment failure, resampling and reevaluation of the tumor should be considered. Performing surgical procedures to reduce the discomfort associated with neoplasm in patients with stable neoplastic disease may significantly improve their quality of life. In palliative patients, the time of anticancer treatment interruptions can be used to tackle their remaining health problems.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Adjuvant radiotherapy in the management of porocarcinoma with lymphatic micrometastasis

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ABSTRACT

Background. Porocarcinoma is a rare skin tumor originating from dermal sweat glands. Surgical procedures are the first choice of treatment, but the role of adjuvant therapies, such as chemotherapy and radiotherapy (RT), is not clear. In this case report and review of the literature, we aimed to present a patient who underwent adjuvant RT for the diagnosis of porocarcinoma with lymphatic micrometastasis and a review of the current literature.

Case summary. A 61-year-old male was admitted to the dermatology department for a nodular lesion on the left knee skin. An excisional biopsy was performed, and the pathology result was reported as porocarcinoma. The closest surgical margin of the tumor was 0.2 cm. In the inguinal sentinel lymph node sampling, two of the three removed lymph nodes had micrometastases. Then, adjuvant RT was applied to the left inguinofemoral lymphatics and primary tumor bed. No recurrence was observed in the patient with a follow-up period of 24 months. No acute or late toxicity was observed including lymphedema, subcutaneous fibrosis, or stiffness of the knee joint.

Conclusions. Although adjuvant RT is not a routinely recommended treatment, it can be applied to increase local and regional control in patients with high-risk factors for recurrence or with lymph node metastases. There is a great need for clinical studies clarifying the role of RT, but for now, all patients should undergo multidisciplinary evaluation when a decision on adjuvant therapies is made.

Key words: porocarcinoma, radiotherapy, skin cancer

Oncol Clin Pract 2023; 19, 2: 124–128

Introduction

Malignant cutaneous adnexal tumors arise from the appendageal apparatus of the skin. Porocarcinoma is an extremely rare malignant appendageal skin tumor. It originates from the intradermal component of dermal sweat gland ducts. The first case was reported in 1963, and since then, only case reports and retrospective studies have been reported [1, 2]. The most common location of malignant cutaneous adnexal tumors is the head and neck region while that of porocarcinoma is the lower extremities, but it can also present at atypical localizations, such as the scalp or breasts [3–5]. It may develop *de-novo* or by malignant transformation of an existing benign poroma [2]. Histopathological examination is essential for a definitive diagnosis. It is generally considered a locally aggressive tumor; however, metastases have also been reported. Surgical excision of the lesion with clear margins is the first choice for treatment. Definitive radiotherapy (RT) may be considered in medically inoperable patients. On the other hand, the role of adjuvant RT is not clear. Sentinel lymph node sampling may be beneficial due to considerably high rates of regional recurrence. The role of systemic therapy is limited to patients with metastatic disease.

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In this case report, we present a patient with the diagnosis of porocarcinoma who underwent adjuvant RT for the primary site and the lymphatic region following sentinel lymph node sampling. We also discuss the role of adjuvant RT.

Case presentation

A 61-year-old male was admitted to the dermatology department in January 2020 due to a nodular lesion on the anterior skin of the left knee that had been present for about three years and had recently grown. His medical history was unremarkable except for laparoscopic prostatectomy without adjuvant treatment for low-risk prostate cancer. Physical examination revealed a nodular lesion measuring approximately 2 cm on the anterior skin of the left knee (Fig. 1). The lesion was excised, and the pathologic finding was reported as porocarcinoma. Histopathological examination revealed nodular masses of epithelial cells in the dermis infiltrating focally into the subcutaneous tissue. Some nodules showed a connection with the epidermis and others necrosis in the center. The stroma was desmoplastic. Nodules were composed of round differentiated poroid cells (Fig. 2). In some areas, pleomorphism, tumor giant cells, and mitoses were remarkable. Carcinoembryonic antigen (CEA) revealed focal luminal staining. CD31 staining did not show lymphovascular invasion. Tumor thickness was 1.35 cm and there were 2 mitoses in 10 high-power fields (2/10 HPF). All surgical margins were clear, but the closest surgical margin of the tumor was the deep surgical margin which was 0.2 cm. Owing to the localization of the tumor bed, wide resection was not performed due to the risk of morbidity related to second-look surgery. Sentinel lymph node sampling was performed via radiopharmaceutical and intraoperative gamma probe for nodal staging, and micrometastases were detected in two of the three removed inguinal lymph nodes. Lymph node dissection was not performed because only micrometastases were detected in the excised lymph nodes of the patient, and the combination of lymph node dissection and adjuvant RT would seriously increase the risk of lymphedema. A positron emission tomography scan (PET-CT) was performed for staging and revealed a parenchymal nodule with the largest diameter of 1 cm in the upper lobe of the right lung. Tru-cut biopsy result of the incidental lung nodule was reported as non-small-cell lung carcinoma. Therefore, the patient underwent lobectomy and mediastinal lymph node dissection for lung cancer. He was staged as pT1N0 according to the eighth edition of the American Joint Commission on Cancer (AJCC) TNM staging system and was followed up without adjuvant chemotherapy or RT.

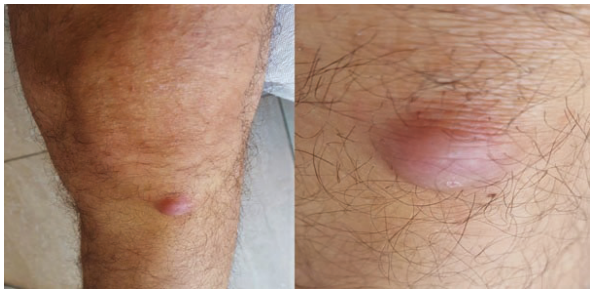

Figure 1. Images of the patient's lesion on the skin of the left knee

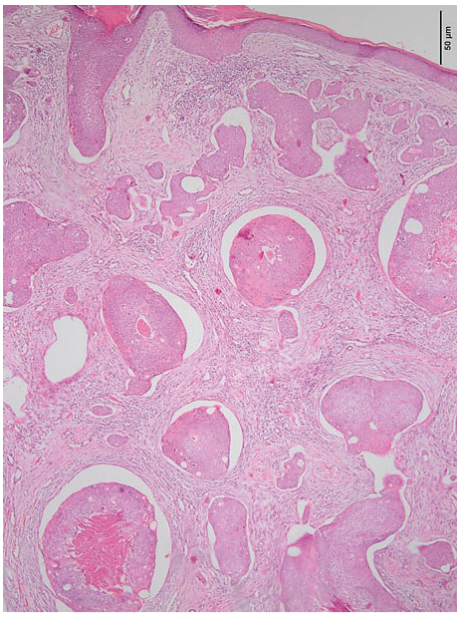

Figure 2. Microscopic image of the tumor. Nodular aggregates of epithelial cells some connected to the epidermis. Separation artifact of nodules from the desmoplastic stroma at the periphery, and necrosis in the center. H.E. ×40

Because of the incidental diagnosis of early-stage non-small-cell lung cancer, adjuvant RT was planned for the primary tumor bed and to inguinofemoral lymphatics five months after excision of the tumor. Since 5 months had passed since the first excision, knee magnetic resonance imaging (MRI) and inguinal ultrasound were performed again, and no residual or recurrent tumor was detected. Then, simulation computed tomography (sim-CT) was performed in the supine position for RT planning. A radiopaque marker was placed on the surgical scar for better delineation of target volumes. The target volumes were contoured by fusion of preoperative MRI and sim-CT. The clinical target volume (CTV) was contoured by giving a safety margin of 3 cm to the preoperative tumor volume. The planning target volume (PTV) was created by giving a 0.3 cm safety mar-

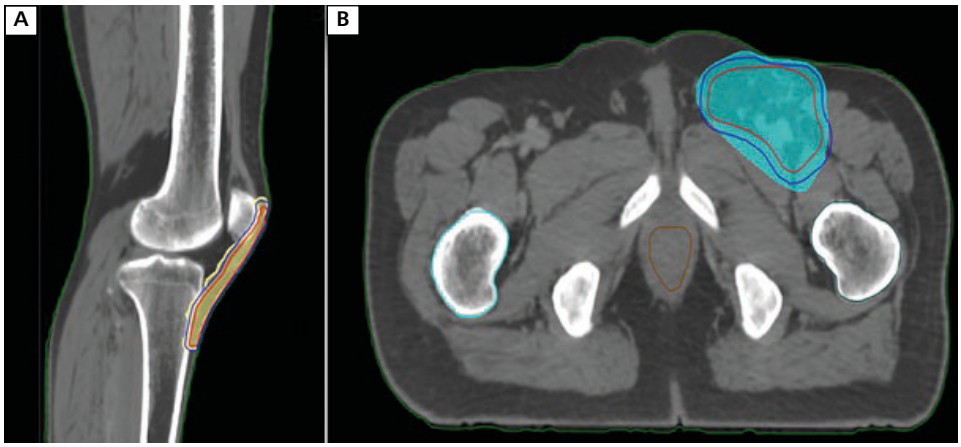

Figure 3. Dose distribution images of the radiotherapy plan; **A.** Sagittal images of the primary tumor bed. Yellow dose color-wash received 59.4 Gy. The red contour is clinical target volume, and the blue contour is planning target volume; **B.** Axial images of the inguinofemoral lymphatic area. Blue dose color-wash received 50.4 Gy. The red contour is clinical target volume, and the blue contour is the planning target volume

gin to the CTV due to the image-guided radiotherapy (IGRT) facility in our department. Volumetric modulated arc therapy (VMAT) of 50.4 Gy in 28 fractions was applied to the primary tumor bed and inguinofemoral lymphatics of the patient with daily cone-beam computed tomography (CBCT). Due to the close surgical margin, five more fractions of RT were applied to the primary tumor bed, increasing the total dose to 59.4 Gy (Fig. 3). The patient used topical moisturizer for dermatitis prophylaxis during RT. Grade 1 dermatitis was observed on the irradiated skin according to common cerminology criteria for adverse events version 5.0 (CTCAE v5.0) during RT. No severe acute toxicity was observed during RT.

After adjuvant RT, the patient was followed up every three months with a complete dermatological examination, inguinofemoral ultrasound, and knee MRI for porocarcinoma, thorax CT every 6 months for lung carcinoma, and blood tests including prostate-specific antigen for prostate adenocarcinoma. No local, regional, or distant recurrence was observed at a follow-up of 24 months. The patient is still under follow-up and is in remission for all three separate malignancies. In addition, no late toxicity was observed in the patient during the follow-up. There was no clinical subcutaneous fibrosis, joint stiffness, or difference in diameters between the lower extremities.

Discussion

Malignant cutaneous adnexal tumors arise from hair follicles and sebaceous, apocrine, or eccrine glands of the skin. Porocarcinoma, also known as eccrine porocarcinoma or malignant hidroacanthoma simplex, is an extremely rare histological variant of these tumors. It originates from the intradermal component of dermal sweat gland ducts. The term of eccrine porocarcinoma was first introduced by Pinkus and Mehregan in 1963 [1]. It constitutes approximately 0.003% to 3.5% of all skin malignancies [6]. Its incidence increases with age and is most common in the 7–8th decades of life. There is no sex predominance. While it is most commonly observed on the skin of the lower extremities, as in our patient, atypical localizations such as the scalp, breasts, and vulva have also been reported [3–5, 7]. Although immunosuppression and some genetic syndromes are blamed in the etiology, there is no clearly defined etiological factor. It may develop as *de-novo* or by malignant transformation of an already existing benign poroma [2].

The rates of local recurrence, regional recurrence, and distant metastasis are around 17%, 19%, and 11% after primary therapy, respectively [8]. Wide local excision is the preferred approach for definitive treatment, but Mohs micrographic surgery is also used with increasing frequency, especially in the head and neck region [9, 10]. In definitive surgery, the primary objective is to obtain a negative surgical margin. There is no clear consensus about the optimal surgical margins for porocarcinoma. Surgical margins between 3 mm and 10 mm have been reported to be effective [11, 12]. In a review of 1968 patients with different subtypes of adnexal carcinomas, it was suggested that the surgical margins should be at least 2 cm after wide local excision. However, due to rarity of the porocarcinoma, it is difficult to conduct studies to generate optimal histology-specific recommendations for surgical margins. Based on these results in the literature, our patient was considered at high risk for local recurrence because the tumor was 0.2 cm away from the closest surgical margin.

Although there is no study comparing definitive RT and surgery, primary RT can be a treatment option in patients medically unfit for surgery or in case of cosmetic concerns. There is limited evidence regarding the role of adjuvant RT in the literature and usually consists of case reports or retrospective reviews. Adjuvant RT in cutaneous adnexal carcinomas is recommended in the presence of high-risk factors such as perineural invasion, lymph node metastasis, extracapsular nodal extension, positive surgical margins, high tumor grade, and recurrent disease [13]. In a study evaluating the clinicopathological characteristics of 69 patients with porocarcinoma, high mitotic index (≥ 14 mitoses per HPF), presence of lymphovascular invasion, tumor depth > 7 mm, and infiltrating type of margins which is defined by malignant clusters infiltrating, and the dermis or hypodermis, instead of pushing type, were reported as negative prognostic factors which are predictive of local recurrence [2]. There are also case reports in which adjuvant RT prevented local recurrence in patients with positive surgical margins [5]. Adjuvant RT doses in the previous reports range from 24 Gy in 12 fractions to 70 Gy in 35 fractions [14]. In our department, we prefer two different fractionation schemes in adjuvant RT for cutaneous adnexal tumors, 50–50.4 Gy in 20–28 fractions or 59.4–60 Gy in 30–33 fractions for patients with R0 resection. In cases with R1 or R2 resection, we apply total doses of 64-70 Gy in conventional fractions.

Regional lymph node dissection (LND) is a common treatment when clinical lymph node metastasis is confirmed, but no survival benefit has been demonstrated. On the other hand, the role of sentinel lymph node sampling (SLNS), which has become a standard procedure in thick malignant melanomas, remains unclear for porocarcinoma. Because of the relatively high rates of lymphatic metastases with porocarcinoma, some authors propose that SLNS should be standardized in the first-line management for optimal staging and decisions on appropriate adjuvant treatments [15, 16]. However, when a micrometastasis is detected in the sentinel lymph nodes the second step in treatment is not clear. LND can be performed; however, the survival benefit is not certain. Besides the lack of survival benefit, LND also increases the risk of lymphedema, particularly in the inguinal region. Considering that regional control can also be achieved with RT in patients with microscopic nodal disease, with breast cancer and malignant melanoma, unnecessary LND and related toxicity can also be prevented with SLNS plus RT in patients with malignant cutaneous adnexal tumors [17, 18]. We achieved good loco-regional control with this approach in our patient, and lymphedema was not observed. However, we think that the decision on treatment for lymph nodes should be made from a multidisciplinary perspective since there is not enough evidence about the effectiveness of RT in patients with particularly macroscopical nodal disease.

The current evidence for adjuvant systemic treatment is based on case reports or retrospective studies, and they are limited only to metastatic patients. Although cutaneous adnexal tumors are considered relatively chemoresistant, there are case reports in the literature showing that satisfactory treatment results are obtained with single-agent or multi-agent systemic treatments, targeted therapies, or hormone therapy agents such as tamoxifen [19, 20]. On the other hand, there are also centers where adjuvant chemotherapy after excision of the primary tumor, is the standard protocol in cases with lymph node metastasis and without distant metastasis [15]. Since our patient had only micrometastatic lymph nodes, adjuvant chemotherapy was not applied, and no distant or regional recurrence was observed at the end of the 24-month follow-up.

Conclusions

Adjuvant RT may have high local control rates in patients with risk factors for recurrence after primary surgery, with minimal toxicity. However, current data are insufficient to support a routine recommendation for the use of adjuvant RT in patients with porocarcinoma, and there is a great need for prospective studies that examine the role of adjuvant RT. Sentinel lymph node sampling may be useful in detecting occult lymph node micrometastases and preventing unnecessary LND. RT alone may be sufficient in patients with occult lymph node micrometastasis detected by SLNS. The adjuvant treatment options in patients with malignant cutaneous adnexal tumors should be discussed in multidisciplinary meetings.

Ethical consideration

Written informed consent was obtained from the patient for the use of his medical information and photographs in an academic article.

Conflict of interest

Authors declare no conflict of interest.

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Epithelioid inflammatory myofibroblastic sarcoma of the lung ALK+/ NTRK+/ PD-L1+

Key words: epithelioid inflammatory myofibroblastic sarcoma, ALK1, NTRK, PD-L1, lung, inflammatory myofibroblastic tumour

Introduction

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a soft tissue neoplasm that represents an aggressive and exceptionally rare subgroup of inflammatory myofibroblastic tumor (IMT). EIMS, as well as IMT, harbor anaplastic lymphoma kinase (ALK) gene fusions; however, recent publications have described different ALK fusion genes involved in EIMS, with particular reference to Ran-binding protein 2 (RANBP2)-ALK fusion. Unlike other neoplasms such as non-small cell lung carcinomas, very little is known about neurotrophic tyrosine receptor kinase (NTRK) and/or PD1/PD-L1 immune checkpoints alterations in such tumors and their value as targets for tailored molecular therapies [1, 2].

Image report

The photos above represent the histological case of a patient in his 20s with a unilateral lung mass and consensual pleural thickening, radiologically strongly indicative of neoplasia.

The histological examination, after surgical resection, shows a proliferation of spindle myofibroblastic cells, in the context of lymphoplasmacytic inflammatory infiltrates and a small amount of eosinophilic granulocytes. The morphologically more aggressive part of the neoplasm (with the presence of mitosis, necrosis, and pleura infiltration), shows epithelioid cytology (Fig. 1A). The immunohistochemistry results are as follows 1) cytokeratins AE1/AE3–; 2) cytokeratins CAM5.2–; 3) cytokeratin 7–; 4) epithelial membrane antigen (EMA)+; 5) Vimentin+; CD31–; CD34–; 6) smooth muscle actin–; 7) specific muscle actin–; 8) desmin–; 9) caldesmon+; 10) pS100–; 11) CD117–; 12) Ki67 10–20%; 13) ALK1+ (Fig. 1B); 14) ALK(clone D5F3)+. PD-L1 expressed in 2–5% in spindle cell areas of IMT and 30–40% in epithelioid areas of EIMS (Fig. 1C); 15) NTRK nuclear expression in scattered cells (Fig. 1D).

The immunomorphological findings are consistent with a pleuro-pulmonary IMT with large neoplastic areas of aggressive evolution into EIMS.

Discussion

To the best of our knowledge, about 60 cases of EIMS have been described and this case represents the fifth primitive pulmonary one [1, 3]. Its topographic location, epithelioid microscopic morphology, immunophenotypic ALK expression, and aggressive features

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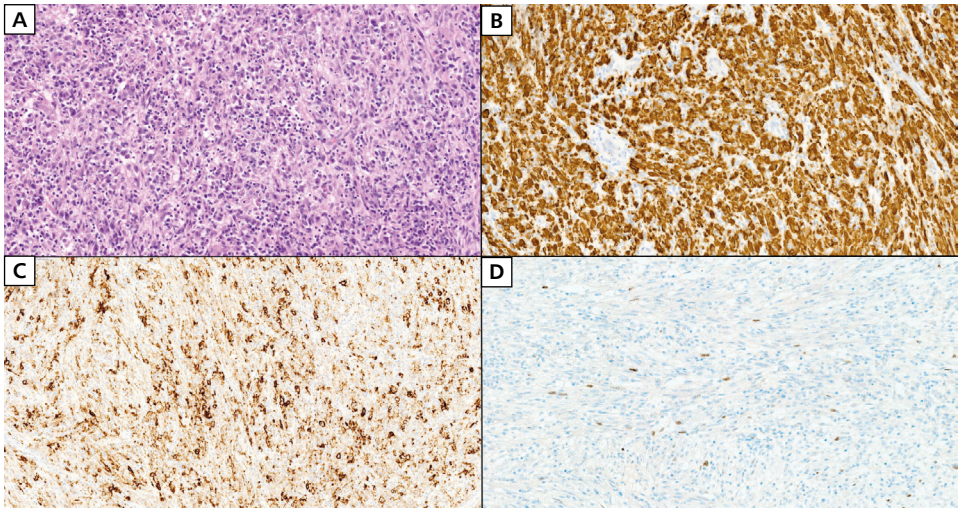

Figure 1. Microphotographs of epithelioid myofibroblastic inflammatory sarcoma (EIMS); A. View of the tumor composed of neoplastic epithelioid cells in an inflammatory background consisting of lymphocytes, plasma cells, and rare eosinophilic granulocytes (Hematoxilin and Eosin, 20×); **B.** Strong and widespread immunohistochemical expression of ALK1 in tumor cells (20×); **C.** High immunohistochemical expression of PD-L1 in neoplastic areas with epithelioid cytology (10×); **D.** Nuclear immunohistochemical staining in scattered neoplastic elements for NTRK (20×)

appear overall consistent with those already reported in the literature.

The one described case was a localized disease, and even microscopically, the surgical margins (both pulmonary and pleural) were free from neoplastic infiltration (staging: R0). In such cases, scarce literature data suggest surgery as the treatment of choice [1]. Therefore, the clinical-oncological decision was made to wait and see, with close follow-up.

In the case of a recurrence, which is reported in about one-quarter of these surgically treated tumors [1], the question will arise whether to treat with new surgery or with oncological therapy. In this context, since chemotherapy appears to have no effect on the progression of EIMS [1], two microscopical findings in our case appear noteworthy: 1) the clear overexpression of PD-L1 in areas with epithelioid morphology (EIMS) compared to those with spindle cells (IMT), and 2) the nuclear expression of NTRK.

These findings, which have been described in rare case reports, have already been the subject of studies about a) the possible interaction between PD-L1 expression and some rare tumor subtypes with rich inflammatory stroma [4]; b) the correlation between ALK molecular pathways and the PD-1/-PD-L1 immune checkpoints [2]; c) the involvement of pathways related to rearrangements of tyrosine kinase receptors [1].

Moreover, such evidence suggests that in addition to therapy with ALK inhibitors (such as crizotinib or the newer brigatinib and lorlatinib), both immunomodulatory drugs and tyrosine kinase inhibitors (TKIs) can be used. However, to date, very little is known about the real efficacy of immune checkpoint inhibitors on IMTs/EIMS (rare reports describe cases treated with nivolumab or sintilimab [1]), while the use of ALK-inhibitors and TKIs is much more established even in the neo-adjuvant phase [5]: hence histologically observed NTRK-positivity may constitute an additional clinically relevant finding as a possible target for specific therapies, e.g. with the use of entrectinib (an NTRK-inhibitor), in this category of tumors.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CLINICAL VIGNETTE

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Management of febrile neutropenia in a breast cancer patient with SARS-CoV-2 infection during dose-dense adjuvant chemotherapy

Key words: febrile neutropenia, SARS-CoV-2, breast cancer, chemotherapy

A 54-year-old woman with clinical stage IIA (pT1c, pN1a, L/V1) invasive poorly differentiated luminal HER2-positive breast cancer [immunohistochemical expression of estrogen receptors 90%, progesterone receptors 50%, Ki67 30%, epidermal growth factor receptor type 2 (3+)] was admitted to the Oncology Department in December 2021 with fever, throat soreness, and pain during swallowing. Symptoms appeared one week after the fourth cycle of dose-dense adjuvant chemotherapy (doxorubicin and cyclophosphamide) with primary granulocyte colony-stimulating factor (G-CSF) support. In March and May 2021, she had received two doses of the mRNA COVID-19 vaccine (Moderna, Spikevax). On admission, she was in fair general condition: Eastern Cooperative Oncology Group Performance Scale grade 1, without dyspnea, oxygen saturation 95% (breathing room air), and the fungal lesions in the oral cavity grade 3 (G3). Common Terminology Criteria for Adverse Events (CTCAE) and Hand-Foot Syndrome G2 CTCAE were observed. The blood test showed leukopenia (G4), agranulocytosis (G4), thrombocytopenia (G2), and an increased level of C-reactive protein (Tab. 1). A polymerase chain reaction analysis (RT-PCR; KIT LabSystem) was performed for SARS-CoV-2 and was positive for the virus core gene (ORF1ab), capsular gene (E), and nucleocapsid gene (N). The blood and urine culture tests were negative. The risk of complications of febrile neutropenia (FN) was assessed at 26 points in the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index [burden of illness as determined by the attending physician at presentation: mild + 5; hypotension systolic blood pressure < 90 mmHg: no + 5; active chronic obstructive pulmonary disease: no + 4; type of cancer: solid tumor + 4; dehydration: + 3; status at the onset of fever: outpatient + 3; age (years): < 60 + 2]. She was admitted to the isolation ward despite being in the low-risk group for poor FN outcome due to clinically significant infection (SARS-CoV-2) and mucosal inflammation G3 (according to the National Comprehensive Cancer Network recommendations). The empiric broad-spectrum antibiotics (ceftriaxone, ciprofloxacin), antifungal drug (fluconazole), G-CSF (filgrastim), intravenous fluids, and probiotics were administered. Due to symptomatic anemia (hemoglobin 7 g/dL), two units of packed red blood cells were transfused. Low-molecular-weight heparin was not considered because of thrombocytopenia (Tab. 1). A chest non-enhanced CT scan was performed in compliance with standard operating procedure (SOP)

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Table 1. Results of laboratory tests performed on days 1, 2, 5, and 8 of hospitalization

	Reference range	1. day	2. day	5. day	8. day
Leukocytes [× 10^9/L]	4.0–10.0	0.09	0.20	2.72	13.09
Neutrophils [× 10^3/μL]	1.9–8.0	0.02	0.11	2.36	11.96
Hemoglobin [g/dL]	11.0–18.0	9.0	7.0	9.2	9.9
Thrombocytes [× 10^9/L]	150–400	54	24	40	68
C-reactive protein [mg/dL]	0.0–0.8	10.4	9.4	5.8	2.7

management in patients with SARS-CoV-2 accepted in December 2021. A moderate level of infiltrate predominantly peripheral in distribution was observed on the chest scan (Fig. 1). On the second day of hospitalization remdesivir was administered with a loading dose of 200 mg intravenously and the next maintenance dose of 100 mg daily for 5 days in total. Therapy was well tolerated with no side effects. After 8 days, the patient in good general condition, with normalization of hematological values and resolution of mucosal inflammation, but with a positive SARS-CoV-2 test, was discharged from the hospital for further isolation at home. After two weeks after the end of hospitalization and after obtaining a negative RT-PCR SARS-CoV-2 test, adjuvant chemotherapy was resumed. The first cycle of paclitaxel 80 mg/m^2 and trastuzumab 8mg/kg was administered. Adjuvant therapy was continued and completed without any other complications.

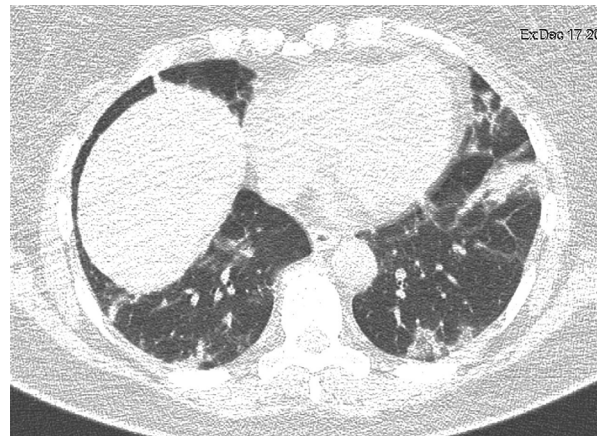

Figure 1. Computed tomography scan of the patient on admission. A moderate infiltrate was observed

Data on febrile neutropenia (FN) management in patients with solid tumors and SARS-CoV-2 infection is limited [1]. Typical treatments of FN are based on empiric or targeted antibiotics, with antifungal drugs (as indicated) and supportive care with strict surveillance of the patient [2]. G-CSF administration in all patients with FN is controversial and applies to specific situations covered by the guidelines [2]. In patients with COVID-19 disease, G-CSF administration may lead to respiratory failure. However, according to European Society for Medical Oncology recommendations, benefits of using G-CSF exceed potential risks [3, 4]. Current data suggest that remdesivir in patients with COVID-19 disease shortens hospitalization and accelerates clinical improvement [5]. In accordance with the Agency for Health Technology Assessment and Tariff System recommendations (3.0 version 28.02.2022), remdesivir therapy should be considered in the high-risk group in the case of a severe course of COVID-19 during virus replication, i.e. sooner than 5 days from the first symptoms of illness, with pneumonia confirmed by medical imaging and oxygen saturation (SpO_2) ≤ 94% (breathing room air). The high-risk group with a severe course of COVID-19 includes also patients with active cancer and immunosuppression (regardless of vaccination status), unvaccinated people, people with suspected insufficient response to vaccination, as well as people with a time from the last dose of the primary series of vaccinations > 6 months [6]. It should be emphasized that this guideline applies to infection with earlier SARS-CoV-2 variants of concern (VC). There is not enough data for reliable recommendations for infection with new SARS-CoV-2 VCs *inter alia* Omikron. Further observations are needed to definitively assess the optimal treatment of patients with FN and SARS-CoV-2 infection.

Conflict of interest

Authors declare no conflict of interest.

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