ISSN 2450–1654 | e-ISSN 2450–6478 2024, Vol. 20, Number 2

Oncology in Clinical Practice 2024, Vol. 20, Number 2, 79–160

OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

Under the patronage of

Polska Grupa Raka Płuca

Polskie Towarzystwo Radioterapii Onkologicznej

VIA MEDICA

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology, under the patronage of the Polish Lung Cancer Group (PLCG) and Polish Society of Radiation Oncology (PSRO)

https://journals.viamedica.pl/oncology_in_clinical_practice

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

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

23-0662.002.001

Editorial Address

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

Indexed in Index Copernicus, Ulrich's Periodicals Directory and CAS. Current Impact Factor of "Oncology in Clinical Practice" (2022) is 0.5.

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

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

ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology, under the patronage of the Polish Lung Cancer Group (PLCG) and Polish Society of Radiation Oncology (PSRO)

https://journals.viamedica.pl/oncology_in_clinical_practice

2024, Vol. 20, Number 2

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) 8th Edition.

1. The aim of the contest is to encourage submission of quality case reports and clinical vignettes related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1, 2023 and May 31, 2024 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 XXVIII 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.

Contest Organizer:
VM Media Group sp. z o.o., seated at 73 Swietokrzyska Street, 80–180 Gdansk, Poland (Register of Entrepreneurs kept by the District Court for Gdansk, Commercial Division VII of the National Court Register under KRS No. 0000266430, VAT Reg. No. PL 583-28-39-187).

Patronage NOVARTIS

Diagnostic and therapeutic management of cancer patients with pain: recommendations of the Expert Group of the Polish Association for Palliative Care, Polish Association for the Study of Pain, and Polish Association of Clinical Oncology

Wojciech Leppert[1, 2], Jerzy Wordliczek[3], Małgorzata Malec-Milewska[4], Magdalena Kocot-Kępska[5], Jarosław Woroń[6], Renata Zajączkowska[3], Jan Dobrogowski[5], Maciej Krzakowski[7], Małgorzata Krajnik[8]

[1]Chair of Palliative Medicine, Institute of Medical Sciences, *Collegium Medicum*, University of Zielona Góra, Poland
[2]University Clinical Hospital in Poznań, Poland
[3]Department of Interdisciplinary Intensive Care, Jagiellonian University *Collegium Medicum*, Cracow, Poland
[4]Department of Anesthesiology and Intensive Therapy, Center for Postgraduate Medical Education, Warsaw, Poland
[5]Department of Pain Research and Therapy, Jagiellonian University *Collegium Medicum*, Cracow, Poland
[6]Department of Clinical Pharmacology, Chair of Pharmacology, Jagiellonian University *Collegium Medicum*, Cracow, Poland
[7]Department of Lung Cancer and Thoracic Tumors, National Oncology Institute of Maria Sklodowska-Curie, National Research Institute, Warsaw, Poland
[8]Chair of Palliative Care, Ludwik Rydygier *Collegium Medicum*, Bydgoszcz, Poland

Table of contents

Received: 11.05.2023 Accepted: 14.05.2023 Early publication date: 20.10.2023

Translation: dr n. med. Dariusz Stencel
Oncol Clin Pract 2024, Vol. 20, No. 2, 79–99, DOI: 10.5603/OCP.2023.0029, Copyright © 2024 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

These guidelines contain evidence-based principles of diagnostic and therapeutic procedures, prepared taking into account the value of scientific evidence and categories of recommendations. The rules of conduct should always be interpreted in the context of the individual clinical situation. Recommendations do not always correspond to the current rules of reimbursement in Poland. In case of doubt, current reimbursement possibilities of individual procedures should be determined. Strength of recommendations and quality of scientific evidence:
I A — Strong recommendation, high-quality evidence
I B — Strong recommendation, moderate-quality evidence
I C — Strong recommendation, low-quality evidence
II A — Weak recommendation, high-quality evidence
II B — Weak recommendation, moderate-quality evidence
II C — Weak recommendation, low-quality evidence

ABSTRACT

In order to elaborate diagnostic and therapeutic recommendations regarding the management of cancer patients with pain, a narrative review of the literature in PubMed and Cochrane database was conducted for the period of 2000–2022. An Expert Group of three scientific associations: Polish Association of Palliative Care, Polish Association for the Study of Pain, and Polish Association of Clinical Oncology was appointed, which made a literature review and formulated guidelines with strength of recommendations and quality of evidence.

To achieve optimal effect of pain treatment cancer patients require complex clinical assessment of pain with detailed recognition of pathophysiology, intensity and time frame (baseline and breakthrough — episodic) of pain. Pain evaluation should encompass other symptoms, comorbidities, disturbances in psychological, social, and spiritual dimensions, which may induce patients' suffering and total pain appearance. An important role plays anticancer local and systemic treatment, which may induce or exacerbate pain induced by cancer or comorbidities.

A standard approach in patients with chronic pain in the course of cancer and other diseases is based on World Health Organization (WHO) analgesic ladder algorithm, which is supplemented with non-pharmacological management. It is recommended an individual approach in pain treatment depending on clinical situation of a concrete patient. Efforts should be made to effectively manage other symptoms, which accompany cancer. An introduction of specific treatment taking into account given pathophysiology, time frame and intensity of pain increase effectiveness and significantly shorten time necessary to achieve effective analgesia, and moreover contribute to decrease intensity and frequency of adverse effects of analgesics used.

Keywords: cancer, clinical assessment, pain, pharmacotherapy, treatment

Oncol Clin Pract 2024; 20, 2: 79–99

Introduction

Pain is one of the most common symptoms in cancer patients. Ensuring the most effective pain management, which is an inalienable right of every patient and, at the same time, the basic duty of every doctor and nurse, allows for maintaining the highest possible quality of life (QoL) for patients and caregivers. According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. The following important characteristics of pain have been distinguished:

— pain is always a personal experience that is influenced to varying degrees by biological, psychological, social, and spiritual factors;
— pain and nociception are different phenomena; pain cannot be inferred solely from activity of sensory neurons;
— through their life experiences, individual learn a concept pain;
— a person's report of an experience as pain should be respected — in Poland, pain therapy is guaranteed by legal provisions ensuring the right to pain treatment for every person;
— although pain usually serves an adaptive role, it may have adverse effects on function, social, psychological and spiritual well-being;
— verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Pain can be differentiated according to its duration (acute *vs*. chronic), pathophysiology (receptor, neuropathic, mixed, nociplastic), and place of sensation (localized *vs*. generalized) [2]. Untreated or ineffectively treated pain is a factor that interferes with proper functioning of the body; pain contributes to the occurrence or intensification of shock symptoms, lowers immunity, and is a factor that significantly reduces patients' quality of life (QoL), which makes effective anti-cancer treatment difficult or impossible and increases the cost of

therapy many times over [3]. Ineffective therapy or lack of pain management can lead to emotional and psychotic disorders as well as depression.

Pain should be considered and treated in the context of a specific clinical situation, taking into account patients' general condition, other symptoms, comorbidities, and anticancer treatment, as well as in the context of non-medical aspects: psychological, social, and spiritual problems of patients and caregivers. The prevalence of pain is estimated at 40–50% of patients undergoing anticancer treatment and 60–70% of patients in an advanced cancer stage [4].

Clinical assessment of pain

Pain is a subjective phenomenon, which is related to individual sensitivity to pain stimuli as well as the multidimensional impact of pain on the physical, mental, social, and spiritual domains. The mental state of patients and their personalities play an important role in the perception of pain [5]. In addition, a significant practical problem is the lack of objective measures of pain; hence its clinical assessment is most often based on the patient's subjective report, and in the absence of self-assessment, on the assessment made by the caregivers and medical staff.

A simple tool for individual assessment of pain intensity is a visual analog scale (VAS), on which the patient indicates the point corresponding to the perceived intensity of pain on a 10-cm continuous line (from no pain to the strongest pain). In clinical practice, the standard tool for assessing pain intensity is the numerical rating scale (NRS), in which the degree of pain severity is defined by the patient with an appropriate number in the range from 0 (no pain) to 10 (the strongest pain). Sometimes a descriptive Likert verbal scale is used to assess pain intensity (no pain, mild pain, moderate pain, severe pain, very severe pain). In children, people who do not know a language, the illiterate, and in patients with cognitive and dyslexic deficits, behavioral pictorial scales are used. Pain intensity should be assessed both before starting treatment and regularly monitored during treatment. A slightly more detailed assessment of pain is provided by the tools adapted to Polish conditions: Memorial Pain Assessment Card (MPAC) and Brief Pain Inventory — Short Form (BPI–SF). The MPAC tool consists of three numerical scales in which the patient assesses pain intensity, pain relief, and general mood and pain intensity is also assessed according to a verbal scale. There is also a section completed by the doctor or nurse, which includes the pathophysiology, location, type of pain (background and breakthrough), and treatment. On the other hand, the BPI–SF contains numerical rating scales for describing pain intensity and pain relief in the last 24 hours, as well as the impact of pain on patients' daily activities during the same period.

Patients with the neuropathic component of pain have various sensory symptoms that may coexist in various combinations. Therefore, clinical examination of patients should include assessment of sensitivity to touch, pricking, pressure, low and high temperature, and vibration, as well as time summation. In recent years, several scales (screening tools) based on verbal description of pain, with or without elements of a clinical examination, have been developed, and they significantly facilitate diagnosis of neuropathic pain and implementation of appropriate treatment. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale consists of five questions about pain and two items of the clinical examination; specificity of the scale is 85%, sensitivity is 80%, and if the number of points is > 12/24, the pain is predominantly neuropathic. Another much simpler Douleur Neuropathique 4 Questions (DN4) scale contains seven symptom questions and three clinical examination items. Specificity of the scale is 83%, and sensitivity is 90%. If the number of "yes" answers is > 4/10, the pain is mainly neuropathic [6].

To assess the nociplastic component, the Central Sensitization Inventory (CSI) questionnaire with 25 questions is used, which has also been translated and adapted to Polish. A score > 40/100 indicates involvement of central sensitization and the nociplastic component of pain [7].

In clinical practice, a useful tool for pain assessment by patients and caregivers can be a diary for regular observation and monitoring of pain treatment, as well as a patient guide on how to manage pain in cancer patients. Both the diary and the guide are available online [8].

Components of pain pathophysiology

The pathophysiology of pain involves two main mechanisms. The first is associated with mechanical and/or chemical activation of pain receptors (nociceptors) and causes nociceptive pain with or without an inflammatory component (somatic, visceral). The second mechanism — independent of the activation of pain receptors — is caused by damage to the somatosensory nervous system and is classified as neuropathic pain. Neuropathic pain is characterized by hyperalgesia (increased sensitivity to pain stimuli) and allodynia (pain caused by stimuli that normally do not cause

pain). Neuropathic pain is often described by patients as burning, stinging, pricking with a tingling sensation, or tearing, often accompanied by sensory disturbances such as hyperesthesia or hypoesthesia or sensations similar to the passage of electric current. It should be emphasized that neuropathic pain is more difficult to treat than nociceptive pain, which is characterized by significantly greater effectiveness of non-opioid and opioid analgesics. It is worth noting that somatic bone pain in cancer patients also shows the characteristics of neuropathic pain; hence it is classified as pain with a neuropathic component. Nociplastic pain is pain that results from changes in the central processes of nociceptive control. It occurs in the absence of clear evidence of actual or impending tissue damage that causes activation of peripheral nociceptors or evidence of disease or damage to the somatosensory system that causes pain [9]. Nociplastic pain is the most difficult to recognize and treat, which may contribute to the ineffectiveness of pain management. In cancer patients, the pathophysiology of pain is usually mixed, with receptor, neuropathic, and nociplastic mechanisms contributing in varying degrees to clinical manifestation.

According to the period of occurrence, pain experienced by patients can be divided into constant, i.e., background (baseline) pain and breakthrough pain, also referred to as episodic pain [10]. Background pain occurs for more than 12 hours a day, while breakthrough pain is defined as an attack of strong and usually short-term pain, with rapidly increasing intensity, despite effectively treated background pain. The time to the maximum intensity of breakthrough pain is usually a few minutes, and the median duration is about 30 minutes, although a pain episode can last from several tens of seconds to several hours. In more recent publications, episodic pain is also diagnosed in patients with ineffectively treated background pain when opioids are not administered or in the absence of background pain. Breakthrough pain can occur without a specific cause (spontaneous, idiopathic pain), or can also be triggered by a specific factor (incidental pain). Breakthrough pain does not include end-of-dose pain, which occurs before the administration of the next dose of a regularly used analgesic and requires correction of background pain treatment [11].

Incidental pain can be divided into independent of the patient's will (involuntary) or dependent on the patient's will (voluntary), i.e., caused by the predictable and voluntary activity of patients or care activities (procedural pain). The strategy for the treatment of spontaneous and incidental involuntary pain consists of administration of analgesics with a rapid onset of analgesic action at the onset of pain to ensure effective analgesia in the shortest possible time. The most used for this purpose are fast-acting fentanyl products, applied by the transmucosal route (nasal, buccal, or sublingual). However, in the case of pain caused by predictable and voluntary activity of patients or care activities (procedural pain), the occurrence of pain should be prevented by applying an additional dose of an analgesic in advance, which will effectively prevent or significantly reduce the intensity of incidental pain. For this purpose, immediate-release opioids can be administered orally or parenterally (subcutaneously, usually at home, or intravenously, usually in stationary or outpatient settings) [12].

General principles of cancer pain management

Whenever possible, treatment of chronic pain should target the underlying condition to achieve permanent relief and prevent other complications. If the cause cannot be identified or eliminated, symptomatic treatment should be used, taking into account the clinical manifestation, especially the pathophysiology, intensity, and time pattern of pain.

Pharmacological treatment

Pharmacotherapy and non-pharmacological methods are used in the management of cancer pain (II A).

In the treatment of background (constant) pain, pharmacotherapy should be conducted continuously to maintain a constant therapeutic blood concentration of drugs, and analgesics should be administered at regular intervals in line with their pharmacokinetic profile, the most convenient route for the patient, with a preference for oral administration. However, if the patient prefers a different route of administration, when oral treatment is not possible, when the patient is taking other drugs that change the bioavailability of analgesics, or when side effects are difficult to treat, analgesics are administered by other routes (transdermal, subcutaneous, intravenous, intrathecal, or topical). It is advisable to use drugs with a long duration of action (oral route with controlled release) and, if necessary (breakthrough pain), drugs with a rapid onset and short duration of analgesic effect (immediate-release oral formulations), which is adequate to the characteristics of breakthrough pain. Frequent breakthrough pain (more than 3 episodes a day) is an indication to consider adjusting the treatment of background pain. An effectiveness of pain therapy should be monitored, and side effects of analgesic therapy should be prevented and treated accordingly.

The use of analgesics is based on the analgesic ladder algorithm developed by the World Health Organization (WHO), according to which analgesics can be divided into three groups [13]. Step I included non-opioid analgesics: non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and metamizole. The next group consists of opioids from step II of the WHO analgesic ladder ("weak" opioids): tramadol, codeine, and dihydrocodeine. At step II of the WHO analgesic ladder, low doses of "strong" opioids may also be used: oxycodone or morphine (at a dose of 20 mg and 30 mg/day, respectively, administered orally). The next group consists of opioids from step III of the WHO analgesic ladder ("strong" opioids): morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, methadone, and hydromorphone (currently unavailable in Poland). Treatment is based on the individual selection of an analgesic adequate to the intensity and pathophysiology of the patient's pain.

Treatment begins with step I drugs (usually with pain intensity corresponds to NRS 1–3). In patients with moderate pain (NRS 4–6), treatment begins with step II or low doses of step III opioids. There is no ceiling effect during treatment with "strong" opioids observed during treatment with step I and II analgesics, which allows the majority of patients to expect a better analgesic effect after increasing the dose of the drug. When using opioid drugs, steps II and III of the WHO analgesic ladder, concomitant administration of non-opioid analgesics may be considered (different mechanism of analgesic effect). However, step II and III opioids should not be combined. At each step of the WHO analgesic ladder, it is advisable to consider the use of supportive agents, which include analgesic adjuvants (co-analgesics) that increase the effect of analgesics and drugs that reduce or prevent their side effects. At each treatment step, there may be indications for the administration of supportive drugs, which include a group of co-analgesics (adjuvant analgesics), increasing the analgesic effects of pain medications in some types of pain (mainly in neuropathic, bone pain and visceral colicky pain) or due to their mechanism of analgesic action in specific types of pain (neuropathic pain, nociplastic pain) and drugs to prevent or alleviate the side effects of opioids (laxatives and antiemetics).

Non-opioid analgesics

They are used alone in mild pain (NRS 1–3) and as supportive agents in pain with moderate (NRS 4–6) and severe (NRS 7–10) intensity, together with opioids.

Table 1. Dosage of non-steroidal anti-inflammatory drugs used in multimodal cancer pain therapy

Drug	Recommended doses
Ketoprofen	100 mg twice a day
Dexketoprofen	3 × 50 mg daily
Ibuprofen	600 mg 4 times a day, the maximum dose is 3200 mg/day
Lornoxicam	First dose 16 mg, then 8 mg 1–2 times a day
Diclofenac	50 mg three times a day or 75 mg twice a day; the maximum daily dose is 150 mg
Nimesulide	100 mg twice daily
Etoricoxib	60–90 mg once daily; the maximum daily dose is 120 mg

Non-steroidal anti-inflammatory drugs (NSAIDs) block prostaglandin synthesis by inhibiting cyclooxygenase (COX) activity and, to a lesser extent, expression of the induced isoform of nitric oxide synthase. They also have non-cyclooxygenase mechanisms of analgesic action; therefore, their choice should be individualized (Tab. 1). Since NSAIDs, except nabumetone, are weak acids and can damage the gastroduodenal mucosa, concomitant use of a proton pump inhibitor (PPI) is recommended in patients at risk. The decision to add a PPI should be individualized, and these drugs should be administered in patients with a clinically significant risk of gastropathy. The use of omeprazole is not recommended due to numerous pharmacokinetic interactions, including with analgesics, and due to the possible side effect on mitochondrial function, which is important in cancer patients. The adverse effect of NSAIDs on the liver is most often manifested by an asymptomatic increase in aminotransferase activity. In particular, administration of diclofenac should be avoided in patients at risk of drug-induced hepatopathy. The adverse effect of NSAIDs on the kidneys may, in turn, lead to peripheral edema and sometimes to acute renal failure. The risk of nephropathy is particularly increased in patients taking concomitant medications that inhibit the activity of the renin-angiotensin-aldosterone system, loop diuretics, and spironolactone. An increased risk of nephropathy may occur with concomitant administration of NSAIDs and paracetamol due to the inhibition of plasma renin activity by paracetamol, and this is of particular importance in dehydrated patients. There is a variable risk of cardiovascular complications associated with the use of NSAIDs; therefore, in this particular group of patients, the choice of NSAIDs should be individualized in relation to the expected analgesic efficacy and

side effect profile. In the case of a clinically significant risk of NSAID-induced adverse effects, especially in the elderly, it is worth choosing drugs with a short peripheral half-life.

Special care should be taken in elderly patients receiving chronic NSAID treatment due to the increased risk of adverse reactions, especially worsening heart failure and renal insufficiency. Rectal administration of NSAIDs is not recommended due to the long latency period of the analgesic effect, and the incidence of side effects is not reduced compared to the oral route. Two systemic NSAIDs should not be administered concomitantly, as this does not increase analgesic efficacy but significantly increases the risk of gastrointestinal mucosa damage and other side effects, but systemic and topical NSAIDs may be combined. NSAIDs are highly effective in the treatment of bone pain, with an inflammatory and receptor component, but are ineffective in neuropathic and nociplastic pain.

Paracetamol has analgesic and antipyretic effects but does not cause peripheral anti-inflammatory effects. At therapeutic doses, NSAIDs class side effects from the gastrointestinal tract and kidneys do not appear; however, paracetamol inhibits plasma renin activity and, especially in dehydrated patients, has a potentially nephrotoxic effect. The clinical effect after administration of paracetamol occurs after 15–30 minutes, depending on the pharmaceutical form of the drug. When using paracetamol in the correct dosage (maximum daily dose 4 g/day), no serious side effects are usually observed, except for allergic skin reactions. At higher doses or with long-term use, side effects may occur, especially in the liver. Paracetamol is contraindicated in patients with liver failure, as well as in patients taking concomitant drugs that are CYP3A4 inducers, e.g., dexamethasone or carbamazepine. When using paracetamol for a long time, special care should be taken in malnourished patients, those abusing alcohol, and using barbiturates and oral anticoagulants. Paracetamol does not cause bronchospasm in people with bronchial asthma. The combination of NSAIDs and paracetamol has a synergistic analgesic and antipyretic effect [14]. Due to its pharmacokinetic and pharmacodynamic profile, paracetamol should not be used in inflammatory pain and visceral pain.

Metamizole is a non-opioid analgesic from step I of the WHO analgesic ladder, devoid of anti-inflammatory effect. The mechanism of the analgesic action is mainly COX2 inhibition in the central nervous system (CNS) and, to a lesser extent, COX1 inhibition and possibly activation of the opioidergic system. This agent has a spasmolytic effect resulting from the central inhibition of adenosine reuptake, which is important in the treatment of acute colic pain and visceral pain. The maximum daily dose of metamizole is 5 g. In cancer patients, the drug is most often used in the treatment of breakthrough, colic and visceral pain. Metamizole should not be administered regularly for more than 7 days due to an increased risk of side effects, especially from the hematopoietic system.

Opioid analgesics

Opioids play a key role in the treatment of moderate to severe cancer pain by affecting three types of opioid receptors: μ, κ and δ, currently referred to as MOR, KOR, and DOR, respectively, and the nociceptin receptor NOR. Opioid receptors are located in numerous structures of the central and peripheral nervous system. The effects of opioids depend on many factors, including an affinity for opioid receptors, effects on the serotonergic, adrenergic, and N-methyl-D-aspartic (NMDA) receptors, as well as on physicochemical properties and pharmacokinetic characteristics. In the treatment of breakthrough pain, the dose of short-acting (immediate-release) opioids administered via an oral route is usually 10–20% of the total daily dose of regularly administered opioids. When using fentanyl with a rapid onset of analgesia via the transmucosal route, the principle of titration from the lowest available dose of a given product always applies. The above rule also applies to the replacement of one fentanyl product with another (also administered by the same route, e.g., intranasally), as well as to significant changes in the treatment of background pain (significant change in the dose of the background opioid or rotation of opioids).

Step II opioid analgesics of the WHO analgesic ladder ("weak" opioids)

Step II opioids of the WHO analgesic ladder are most often used in patients with moderate pain (NRS 4–6) [15]. Exceeding the recommended maximum doses usually does not cause an additional analgesic effect but may intensify side effects ("ceiling effect"). Tramadol, codeine, and dihydrocodeine are available in Poland (Tab. 2).

Tramadol is the most commonly used step II opioid of the WHO analgesic ladder, with an analgesic effect several times weaker than that of morphine (II A). Tramadol exhibits a dual mechanism of analgesic action: in addition to acting on opioid (predominantly μ) receptors in the CNS, it activates the descending antinociceptive system by inhibiting the reuptake of norepinephrine and serotonin. Tramadol is metabolized in

Table 2. Most commonly used opioids in the treatment of cancer pain

Drug	Route of administration, drug form	Starting dose, comments	Duration of action [hours]
Morphine	Oral: Divisible tablets 20 mg, aqueous solution	Primarily intended for dose titration and treatment of breakthrough pain Patients not treated with opioids: 2.5–5 mg every 4–6 h Patients treated without effect with "weak" opioids: 5–10 mg every 4–6 h In the treatment of breakthrough pain, usually 10–20% of morphine daily dose	4–6
	Controlled-release tablets 10, 30, 60, 100, and 200 mg	Opioid-naïve patients: usually 10 mg every 12 hours Patients treated without effect with "weak" opioids usually 20–30 mg every 12 hours	12
	Subcutaneous and intravenous: morphine sulphate ampoules 20 mg/1 mL	Subcutaneous route: Usually 2–3 mg every 4–6 h in patients not treated with opioids, most often 4–6 mg every 4–6 h in patients treated without effect with "weak" opioids	4–6
		Intravenous route: Usually 1–2 mg every 4–6 h in patients not treated with opioids, most often 3–5 mg every 4–6 h in patients treated without effect with "weak" opioids If necessary, the dose may be increased and repeated every few minutes until pain subsides or sedation occurs. Usually used to quickly obtain analgesia both in hospital and outpatient settings	4
Oxycodone	Oral: 1 mg/1 mL aqueous solution (100 mL and 250 mL), 5 and 10 mg tablets	Primarily intended for dose titration and treatment of breakthrough pain Patients not treated with opioids: 2.5–5 mg every 4–6 h Patients treated without effect with "weak" opioids: 5–10 mg every 4–6 h In the treatment of breakthrough pain, usually 10–20% of oxycodone daily dose	4–6
	Controlled-release tablets 5, 10, 20, 40, 60, and 80 mg	Patients not treated with opioids usually 5–10 mg every 12 hours Patients treated without effect with "weak" opioids usually 10–20 mg every 12 h	12
	Subcutaneous and intravenous: oxycodone hydrochloride 10 mg/1 mL and 20 mg/2 mL ampoules	Subcutaneous route: Usually 2–3 mg every 4–6 h in patients not treated with opioids, most often 4–6 mg every 4–6 h in patients treated without effect with "weak" opioids	4–6
		Intravenous route: Usually 1–2 mg every 4–6 h in patients not treated with opioids, most often 3–5 mg every 4–6 h in patients treated without effect with "weak" opioids If necessary, the dose may be increased and repeated every few minutes until pain subsides or sedation occurs. Usually used to quickly obtain analgesia both in hospital and outpatient settings	4
Tramadol	Oral: Drops (40 drops = 100 mg, drops with dispenser 1 dose = 5 drops)	Drops are useful, especially during the titration period and for the treatment of breakthrough pain 5–20 drops (12.5–50 mg) every 4–6 hours For breakthrough pain, usually 10–20 drops, depending on the dose administered regularly, for the treatment of background pain	4–6
	50 mg capsules Controlled-release tablets and capsules of 50, 100, 200 mg	Controlled-release tablets or capsules of 50–100 mg every 12 h	12
	Subcutaneous and intravenous: tramadol hydrochloride (50 mg/1 mL, 100 mg/2 mL ampoules)	Subcutaneous route: usually 20–50 mg every 4–6 h	4–6

→

Table 2 cont. Most commonly used opioids in the treatment of cancer pain

Drug	Route of administration, drug form	Starting dose, comments	Duration of action [hours]
		Intravenous route: usually used both in hospital and outpatient settings, the most common dose is 50–100 mg in slow infusion The maximum dose of tramadol is 400 mg/day Dual (opioid and non-opioid) analgesic mechanism, less frequent constipation as compared to other opioids Prophylactic addition of an antiemetic drug (haloperidol or tiethylperazine) is recommended when starting treatment with tramadol. Analgesia and side effects (mainly related to the opioid component) dependent on CYP2D6 polymorphism	4
Codeine	Oral: 20 mg tablets, aqueous solution	The maximum dose of codeine is 240 mg/day Codeine is largely a prodrug: partially metabolized to morphine by CYP2D6 Analgesia and side effects of codeine are dependent on CYP2D6 polymorphism	4–6
Dihydro-codeine	Oral: Controlled-release tablets of 60 and 90 mg	The starting dose is usually 1–2 × 60 mg, the maximum dose of dihydrocodeine is 240 mg/day Analgesia and side effects of codeine are dependent on CYP2D6 polymorphism	12
Fentanyl	Transdermal: 12.5, 25, 50, 75, and 100 μg/h patches	The starting dose is 12.5–25 μg/h in patients not treated with opioids and 25 μg/h in patients treated with "weak" opioids; the maximum dose is 200 μg/h No active metabolites, drug metabolized by CYP3A4	72
Bupreno-rphine	Transdermal: 35, 52.5, and 70 μg/h patches	The starting dose is usually 17.5 μg/h in opioid-naive patients and 35 μg/h in patients treated with "weak" opioids; the maximum dose is 140 μg/h Drug metabolism mainly by glucuronic acid conjugation, excreted mainly via the gastrointestinal tract, preferred in stable neuropathic pain, in elderly patients, and in renal impairment	72–96
Oxycodone/ /naloxone	Oral: Controlled-release tablets 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20mg	Patients not treated with opioids 5 mg/2.5–10 mg/5 mg every 12 h. Patients treated without effect with "weak" opioids 10 mg/5 mg every 12 h In the treatment of breakthrough pain, usually 10–20% of oxycodone daily dose Patients treated with other "strong" opioids: the dose is determined individually through equivalent dose converters and titration. The maximum dose is 80 mg/40 mg twice a day	12
Tapentadol	Oral: Controlled-release tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Patients not treated with opioids 50 mg every 12 h Patients treated without effect with "weak" opioids 50–100 mg every 12 h The maximum dose is 250 mg twice a day	12

the liver by cytochrome P–450, and then approximately 90% (after oral administration) is excreted via the kidneys, with approximately 10% excreted in feces. The analgesic effect of tramadol depends on the activity of the CYP2D6 enzyme. It catalyzes the conversion of the parent compound to O-desmethyltramadol (M1), which has a significant analgesic effect by activating μ-opioid receptors. In the Caucasian population, 7–10% of people do not metabolize of tramadol to M1 (poor metabolizers), then the analgesic effect may be much weaker, while 1–2% excessively metabolize tramadol to M1 (ultrarapid metabolizers). This results in a higher risk of side effects, including nausea and vomiting, sedation, and respiratory depression.

The most commonly observed side effects associated with the use of tramadol are nausea and hyperhidrosis, especially at the beginning of treatment. The advantage of tramadol is a lower impact on the motility of the gastrointestinal tract and a weak constipation-inducing effect, as well as a lower risk of causing respiratory

depression compared to other opioids. Tramadol is available in many formulations, including a controlled release form. Tablets, oral drops (40 drops = 100 mg), and ampoules are used, which can be administered subcutaneously and intravenously. The drug should be used in doses up to 400 mg/day, administered in the immediate-release formulations every 4–6 hours, or in prolonged-acting forms every 12 hours. In breakthrough pain during treatment with tramadol as a background drug, immediate-release preparations of tramadol are used. Tramadol is available as a fixed-dose combination (FDC) with paracetamol and dexketoprofen, which accelerates the onset of action of the drug and causes a synergistic analgesic effect.

Due to the prolonged half-life of tramadol and its being an active metabolite in patients with renal failure, it is recommended to reduce its dose and to extend the intervals between subsequent doses or to switch to another opioid. Extending the dosing intervals and reducing the dose is also recommended in patients with hepatic impairment. In patients with a history of epilepsy, tramadol is not recommended due to an increased risk of seizures, and in patients without a history of epilepsy, the drug does not increase the risk of seizures. Due to an increase in the concentration of porphyrins, tramadol raises the risk of attacks in patients with acute porphyria. Tramadol should not be administered together with antidepressants that inhibit the reuptake of serotonin, as well as serotonin and norepinephrine, and tricyclic antidepressants, as it may lead to symptoms of serotonin syndrome. The use of tramadol with CYP3A4 inducers (mainly carbamazepine or dexamethasone) is contraindicated because an increased amount of N-desmethyltramadol is synthesized, which has no analgesic effect but has a proconvulsant effect. In the case of concomitant use of CYP2D6 inhibitors with tramadol, the risk of nausea and vomiting increases significantly, and the simultaneous administration of tramadol and carbamazepine worsens its analgesic effect.

Codeine is an agonist of the μ-opioid receptor, with an analgesic effect approximately 10 times lower than that of morphine. Codeine is a prodrug with an analgesic effect dependent on the conversion to morphine determined by the activity of CYP2D6, as well as other metabolites (mainly codeine-6-glucuronide). Due to its strong antitussive properties, it is considered the drug of choice in patients with moderate pain and cough. A common side effect of codeine is constipation. Codeine is only administered orally in the form of immediate-release tablets or solution. The analgesic effect occurs after 15–30 minutes and lasts for 4–6 hours ($T_{1/2}$ 3–4 hours). The maximum daily dose of codeine is 240 mg. Codeine is also available in FDC with paracetamol, paracetamol and caffeine, acetylsalicylic acid and ibuprofen. Due to its pharmacokinetic profile and genetically variable metabolism, codeine is not recommended for the treatment of pain.

Dihydrocodeine (DHC) is a derivative of codeine. The analgesic potency of DHC is approximately 5 times weaker than that of morphine administered via an oral route. The drug is metabolized mainly to DHC-6-glucuronide and dihydromorphine, and side effects are usually less severe compared to codeine. Unlike codeine and tramadol, the analgesic effects of DHC do not depend on CYP2D6 activity. Dihydrocodeine is only available as controlled-release tablets to be taken every 12 hours. The maximum daily dose of DHC is 240 mg. DHC is recommended in patients with moderate pain, often accompanied by cough and shortness of breath.

A common feature of tramadol and codeine metabolism is the dependence of the analgesic effect and side effects on the genetically determined CYP2D6 activity, as well as renal excretion (the latter also applies to DHC), while the analgesia and side effects of DHC do not depend on CYP2D6 activity. At step II of the WHO analgesic ladder, low doses of "strong" (morphine up to 30 mg, oxycodone up to 20 mg per day orally) can be used instead of "weak" opioids [16].

Step III opioid analgesics of the WHO analgesic ladder ("strong" opioids)

Opioids without the ceiling effect from step III of the WHO analgesic ladder are recommended for the treatment of severe and very severe pain (NRS 7–10) [17]. Morphine, oxycodone, oxycodone/naloxone, fentanyl, buprenorphine, tapentadol, and methadone are available in Poland, and hydromorphone is not available yet [18]. According to the European Association for Palliative Care (EAPC) guidelines, morphine, oxycodone, and hydromorphone are the first-choice opioids in the treatment of moderate to severe cancer pain (I A) [13]. In the treatment of chronic pain, the use of pethidine and pentazocine is contraindicated due to the toxic effects of their metabolites.

Morphine is the standard opioid recommended by the WHO and the European Society for Medical Oncology (ESMO). The strength of the analgesic effect of other opioids is compared to morphine (I A). It is a pure agonist of opioid (predominantly μ) receptors. The main metabolites are morphine-3-glucuronide and morphine-6-glucuronide, and, like the parent compound, they are excreted by the kidneys. Morphine is a hydrophilic opioid of choice in the treatment of pain and in patients with dyspnea [19]. Concomitant use of

morphine and benzodiazepines, and other CNS depressants increases the risk of sedation, hypotonia, and respiratory depression. Constipation may be a significant problem during treatment with morphine [20]. Many drugs taken concomitantly with morphine, including drugs with anticholinergic effects (e.g., pridinol and tizanidine) and serotonin receptor antagonists, also increase defecation disorders.

In the treatment of pain, morphine is used orally with immediate- and controlled-release formulations or parenterally (subcutaneously, intravenously), rarely intrathecally and topically. The equivalent oral dose is approximately 3-fold higher than the parenteral dose due to limited absorption from the gastrointestinal tract and significant hepatic first-pass effect. Treatment usually starts with low single doses (tablets, less often water solution with immediate release), usually 5 mg (patients not previously treated with "weak" opioids) or 10 mg (patients previously treated with "weak" opioids), administered every 4–6 hours. In the case of starting morphine treatment with controlled-release tablets in patients previously untreated with "weak" opioids, a single dose of morphine of 10 mg every 12 hours is most often used (20 mg daily), while treatment of patients previously receiving "weak" opioids usually starts with a single dose of 20 or 30 mg every 12 hours (daily dose is 40 mg and 60 mg, respectively). Sometimes administration of controlled-release morphine is recommended every 8 hours. The initial doses given in patients with renal impairment, severe cachexia, and the elderly are usually half as low. In these groups of patients, due to reduced elimination of morphine metabolites, close monitoring is required, and sometimes also prolongation of the intervals between subsequent administrations of the drug, change of administration route to parenteral, or switch (rotation) to another opioid. Moderate liver damage does not significantly affect the metabolism of the drug.

Morphine product, dose, and administration route are determined individually, using the principle of gradually increasing doses until a satisfactory analgesic effect with side effects acceptable to the patient is obtained (titration). During the treatment of background pain with controlled-release morphine, immediate-release morphine products are used in the treatment of breakthrough pain, usually in a dose equal to approximately 10–20% of the daily dose. During the treatment of background pain with immediate-release morphine, the dose administered in the treatment of breakthrough pain is usually equal to a single dose administered every 4–6 hours [21]. In patients in whom morphine is regularly used subcutaneously or intravenously, the rescue dose is most often administered by the same route and is usually equal to a single dose.

Oxycodone is a semi-synthetic μ and k receptor agonist (I A). Unchanged oxycodone and its metabolites are mainly excreted via the kidneys, which requires careful use of the drug in cases of impaired renal function [22]. Oxycodone is administered orally or parenterally (subcutaneously or intravenously) [23]. The morphine-to-oxycodone equivalent dose ratio is 1.5–2:1 for the oral route. When switching from parenteral to oral oxycodone administration, a 3:4 ratio is applied, i.e., the oral dose is slightly higher than the parenteral dose. Controlled-release oxycodone tablets are given every 12 hours. During oxycodone treatment, oxycodone or immediate-release morphine or transmucosal fentanyl products can be used as the primary treatment for breakthrough pain.

Oxycodone/naloxone is a 2:1 combination of oxycodone and naloxone in one controlled-release tablet (I B). In clinical trials, the product was shown to be effective in the treatment of chronic cancer pain and pain in the course of non-cancerous diseases while improving or preventing opioid-induced constipation [24]. The recommended daily dose cannot exceed 160 mg/80 mg and should be achieved gradually by titration [25]. Contraindications to the use of oxycodone/naloxone are typical of opioids; however, hepatic, renal, and portal circulation disorders, allergy to the product's ingredients, and diarrhea are also important.

Fentanyl is a pure μ-opioid receptor agonist. Its analgesic strength compared to morphine is approximately 100:1. The significant lipophilicity of the drug is used in transdermal and transmucosal therapy. Fentanyl is metabolized in the liver by CYP3A4 to the inactive norfentanyl and then excreted by the kidneys mostly (90%) as inactive metabolites. It is well tolerated by patients with moderate hepatic and renal insufficiency. The use of transdermal and intravenous fentanyl is quite safe in advanced chronic kidney disease (grades 4–5) with a glomerular filtration rate below 30 mL/min. Compared to morphine, fentanyl has a less pronounced sedative effect, releases histamine to a small extent, and less frequently causes constipation [26].

For the treatment of pain, fentanyl is administered by the transdermal, transmucosal, and parenteral routes. Transdermal patches are applied every 72 hours, with the analgesic effect about 12 hours after applying the first patch, and full analgesic effectiveness is achieved after 2–5 changes of patches (II B). Particular care should be taken in patients with fever due to the increased rate of absorption and release of the drug and, consequently, the increased risk of side effects.

Table 3. Fentanyl products used to treat breakthrough pain episodes

Selected pharmacokinetic parameters	Route of administration			
	Sublingual (tablets)	Buccal (tablets)	Intranasal (nasal spray)	Intranasal (nasal spray with pectin)
Absolute bioavailability [%]	70	65	89	60
Time to peak serum concentration [minutes]	50–90	47	9–15	15–21
Half-life [hours]	12	22	3–4	15–25
Onset of analgesic effect [minutes]	5–10	10–15	5–7	5–10

In the treatment of breakthrough pain during therapy with transdermal fentanyl and other opioids, intranasal formulations, or buccal/sublingual fentanyl tablets with a rapid onset of analgesic effect can be used (Tab. 3) [27]. The general principle of use of transmucosal fentanyl products is dose titration, which also applies when changing the type of fentanyl formulation (e.g., from intranasal to buccal or vice versa or between different intranasal products) and after switching from using other traditional opioids for breakthrough pain (e.g., short-acting morphine or oxycodone). According to SPC rapid-onset fentanyl products can only be recommended to cancer patients who are using opioids to treat their background pain (daily dose of oral morphine of 60 mg or equivalent dose of morphine administered by other routes or an equivalent dose of other opioids, used for at least 7 days). During therapy with transdermal fentanyl, oral immediate-release morphine or morphine administered by other routes (subcutaneous, intravenous) may also be used for breakthrough pain management. The choice of transmucosal administration route of fentanyl for the treatment of breakthrough pain should be based on clinical assessment of pain exacerbation characteristics, condition of the nasal and oral mucosa, and the patient's preferences. Fentanyl has a serotonergic effect, which is worth remembering, especially in polytherapy.

Buprenorphine is a partial agonist of μ-opioid and nociceptin receptors and an antagonist of the κ-opioid receptor. The potency of buprenorphine is approximately 75 times greater than that of morphine. In the analgesic therapeutic dose range, buprenorphine acts as a pure μ-opioid agonist and shows no ceiling effect. Drug metabolites are excreted in 70–80% by the digestive tract and a small amount by the kidneys. Buprenorphine is a safe opioid in patients with chronic renal failure and in dialysis patients. It is rapidly absorbed through the oral mucosa and is used in the form of sublingual tablets administered every 6–8 hours as it is poorly absorbed from gastrointestinal tract. Due to its high lipophilicity, the drug is administered transdermally as patches applied to the skin every 72–96 hours (II B). The analgesic effect of the first buprenorphine patch occurs after about 12 hours [28]. Oral or subcutaneous morphine or fentanyl fast-acting products are most commonly used for the treatment of breakthrough pain during background therapy with transdermal buprenorphine [29]. Buprenorphine patches are the only "strong" opioid available on Rp prescriptions.

Tapentadol is a representative of a new group of opioid analgesics with a complex mechanism of action: agonistic effect on opioid receptors, predominantly μ, and inhibition of norepinephrine reuptake in the CNS (I B). Due to the complex mechanism of analgesia, tapentadol has an analgesic effect typical of opioids and antidepressants from the group of norepinephrine reuptake inhibitors [30]. In addition to effective analgesia, including in patients with neuropathic pain, tapentadol is characterized by good treatment tolerance. Compared to other opioids, it is associated with limited side effects related to the influence on opioid receptors (particularly important in terms of the adverse impact on the gastrointestinal tract), low risk of interactions with other drugs (metabolism outside the cytochrome P–450 enzyme system), and lower potential for addiction [31].

Methadone is a synthetic μ and κ opioid receptor agonist, NMDA receptor antagonist that increases monoamine levels (I A). The analgesic potency, compared to oral morphine, is 4–12-fold higher. Methadone causes less severe constipation, nausea, and vomiting and it can be safely used in chronic renal failure and dialysis patients. Due to the complex pharmacokinetics, significant risk of drug interactions, and prolongation of the QT interval, it is recommended that methadone treatment should be conducted by a physician experienced in pain management. The drug is used orally in the form of syrup (concentration 1 mg/1 mL),

administered every 12 hours at a single initial dose of 2.5–5 mg. It is recommended not to exceed the initial daily dose of 10 mg in patients who have not previously been treated with other strong opioids. In patients who fail to achieve an adequate analgesic effect or experience severe side effects during treatment with other opioids, it is suggested to consider switching to methadone [32]. Methadone is used not only in the treatment of chronic pain but also in the treatment of opioid addiction and withdrawal syndromes.

Side effects of opioid analgesics

An individual system of opioid receptors in each person may be the cause of a different analgesic effect of opioids and different profiles and severity of side effects [33]. The most commonly observed side effects of opioids include constipation and other post-opioid gastrointestinal disorders. From the beginning of treatment with opioids, it is usually necessary to use prophylactic osmotic laxatives orally: macrogol or, less frequently, lactulose (due to it having more side effects) alone or in combination with irritants: senna derivatives, bisacodyl, and sometimes rectal irritants, e.g., glycerin suppositories.

The drugs of choice in the treatment of opioid-induced bowel dysfunction (OIBD) are peripherally acting μ-opioid receptor antagonists (PAMORA), such as naldemedine, N-methylnaltrexone, and naloxegol. Nausea and vomiting are less frequently observed side effects of opioids, and metoclopramide, haloperidol, and thiethylperazine are the most commonly used in their treatment. Metoclopramide, due to the inhibition of CYP2D6 activity, should not be administered in patients taking tramadol concomitantly and other drugs with hepatic clearance dependent on cytochrome P450 isoenzyme. Other side effects of opioids include drowsiness, dry mouth, balance disorders, skin itching, excessive sweating, hallucinations, respiratory depression (rare, most often associated with improper opioid dosing), urinary symptoms (urinary retention), myoclonus, and very rarely seizures. In the case of respiratory depression, intravenous naloxone should be administered (1 amp = 400 μg should be diluted in 10 mL of saline and administered 40–80 μg, i.e., 1–2 mL, every 30–60 seconds until opioid overdose symptoms subside).

In the case of opioid side effects, four strategies are commonly used: reducing the dose of systemically administered opioids, symptomatic treatment adequate to complication pathophysiology, changing the route of opioid administration, and rotation (switching) of opioids. The concept of opioid rotation means changing the currently used opioid analgesic to another opioid. Opioid replacement enables the elimination of metabolites, which may be important in patients treated with morphine who suffer from deterioration of renal function or dehydration. Similarly, in the case of analgesic inefficacy during treatment with one opioid, a switch to another opioid should be made. Due to incomplete cross-tolerance, care should be taken when converting the corresponding doses of different opioids, and lower converters should be used than those resulting from tables of equivalent doses of opioids, whose usefulness in clinical practice is limited. In each case, the patient requires determination of additional dose — single and daily — and close monitoring during titration to achieve an effective dose. In most patients, switching to opioids improves the effectiveness of pain management and reduces side effect intensity. Occasionally, two-step III opioids are administered simultaneously (e.g., morphine or oxycodone with fentanyl or buprenorphine), which is based on slightly different binding to receptor subtypes and differences in physicochemical properties of different opioids. There are no guidelines in this regard due to the small number of clinical trials conducted so far.

Supportive agents and adjuvant analgesics

Supportive agents are recommended at every step of the WHO analgesic ladder and include adjuvant analgesics (co-analgesics) that relieve pain or enhance the analgesic effect of other analgesics as well as drugs that prevent or treat side effects of opioids (laxatives, antiemetics). While analgesics are selected according to the intensity of pain, in the selection of adjuvant analgesics, attention is paid mainly to the specific pathophysiology of pain. Adjuvant analgesics are particularly useful in the treatment of pain with neuropathic, nociplastic, and bone components (Tab. 4) [34]. Antiepileptic drugs are most commonly used — mainly gabapentinoids (gabapentin, pregabalin, mirogabalin), less often older drugs: valproic acid, clonazepam, carbamazepine (I A). In addition, antidepressants, norepinephrine and serotonin reuptake inhibitors (venlafaxine in a daily dose of 150–225 mg, duloxetine, milnacipran), some of selected selective serotonin reuptake inhibitors (SSRIs) — vortioxetine and tricyclics (amitriptyline) are frequently used (I A). Other classes of medications used to treat neuropathic pain include topical medications (lignocaine and capsaicin) (II C) and systemic NMDA blockers (ketamine and dextromethorphan) (II B). In bone pain, NSAIDs (II A), bisphosphonates, and denosumab are most often used; moreover, due to the frequent component of neuropathic pain, antiepileptic drugs (usually pregabalin and gabapentin) are sometimes considered [35]. In the treatment of neuropathic

Table 4. Most commonly used adjuvant analgesics in the treatment of cancer pain

Drug group	Drug	Dosage, comments	Duration of action [hours]
Anticonvulsants	Pregabalin	Initially, 2 × 25–75 mg, maximum dose 2 × 300 mg, the starting dose depends on the patient's age and treatment tolerance in terms of emerging potential side effects The drug of first choice from the group of analgesic adjuvants due to the pharmacokinetic and pharmacodynamic profile most often added to opioids because of the lack of a full analgesic effect. Used to treat general anxiety	9–12
	Gabapentin	Initially 3 × 100–200 mg, most often the dose is gradually increased to 900––2400 mg/day; doses > 3600 mg/day are not recommended	8
	Valproic acid	Initially, 2 × 300 mg, recommended doses are 2 × 500 mg, do not exceed a daily dose of 1500 mg; the drug is available in liquid oral form and intravenous form	16–24
Anti-depressant	Duloxetine	The starting dose is usually 1 × 30–60 mg (effective doses 60–120 mg), if necessary, increased to 1 × 120 mg. Due to CYP1A2 induction, lower efficacy may be required, and higher doses may be required in smokers (AUC lower by 50%). Co-administration of CYP1A2 and CYP2D6 inhibitors with irreversible MAOIs is not recommended. It may increase blood pressure	16–24
	Venlafaxine	The starting dose is 1 × 37.5–75 mg; it should be increased to 150–225 mg (in this range, it inhibits the reuptake of serotonin and norepinephrine; in lower doses, it is only SSRI). Metabolized by CYP2D6 to the major active metabolite O-desmethylvenlafaxine and CYP3A4 to N-desmethylvenlafaxine. In combination with sympathomimetic drugs has a cardiotoxic effect	12
	Amitriptyline	Starting dose 1 × 25 mg, titrated up to 1 × 75 mg if necessary. Metabolized by CYP2D6 to the active metabolite nortriptyline, which has a long and variable half- life (20–100 h). It has a strong antimuscarinic and antihistamine effect and numerous side effects	24
Glucocorticoids	Dexamethasone	Dosage is usually 4–16 mg once a day or in two divided doses, an anti-inflammatory effect most often used in the short-term treatment of bone pain and nerve compression, numerous indications in emergencies and supportive therapy, given as a component of anticancer treatment in some tumors	36

AUC — area under the curve; MAO — monoamine oxidase inhibitor; SSRI — selective serotonin reuptake inhibitor

pain caused by nerve compression and bone pain, glucocorticoids are used, especially in the case of involvement of the respiratory system and the coexistence of dyspnea, liver tumors, and brain metastases [36]. Due to the pharmacokinetic-pharmacodynamic profile, dexamethasone is particularly indicated. Attention should be paid to observing the rules of careful dosing (titration) of adjuvant analgesics, especially in combination with opioids, which allows for avoiding or at least significantly reducing the risk of side effects.

Non-pharmacological pain management

In some cancer patients, severe pain is not always effectively relieved by pharmacological treatment alone. In these patients, non-pharmacological methods are used, including anticancer treatment (systemic and local: radiotherapy and surgery), interventional methods, physiotherapy, acupuncture, physical exercise, and psychological support [37]. Radiation therapy is effective in bone pain, which in 60–80% of patients causes a significant reduction or complete resolution of pain, and the analgesic effect often lasts for many months. In some patients different procedures are used, including orthopedic operations, surgical immobilization (stabilization), vertebroplasty (in the case of pathological fractures of vertebral bodies), blocks of musculoskeletal system structures, nerve plexuses and peripheral nerves, neurodestructive procedures (neurolysis, cryolesia, thermolesion) within the nervous system and the administration of analgesics and/or adjuvant analgesics by intrathecal route (subarachnoid or extradural). Due to the complex etiology of pain and occurrence of total pain, many patients require psychological, social, and spiritual support.

Physiotherapy

Physiotherapy should be considered at every stage of cancer pain management as an element of multimodal therapy. In some patients, especially the elderly, the type of physiotherapy should be adapted to their physical capacity and capabilities [38]. Most often, indications for the use of physiotherapy include:

— myofascial pain — after treatment (changes in body posture, scars), abnormal movement patterns, immobilization, increased muscle tension caused by pain;
— bone pain caused by metastases;
— neuropathic pain during and after anticancer treatment.

Techniques used to treat myofascial pain in cancer patients include:

— trigger point therapy (palpable points present within a tense muscle band, hypersensitive to mechanical stimulation);
— mechanical methods — joint mobilization, neuromobilization;
— physical treatments;
— techniques of proprioceptive neuromuscular facilitation (PNF);
— kinesiotaping.

Therapeutic techniques used in patients with bone pain and the role of the physiotherapist include:

1. patient and family education:
— learning to change positions, belying while moving,
— assistance in the selection and use of rehabilitation equipment;
2. neuromodulation techniques — transcutaneous electrical nerve stimulation (TENS).

Transcutaneous electrical nerve stimulation is a cheap and easily accessible method, which can also be performed at home, and side effects are rare (allergic skin reactions, skin burns, edema, pain intensifying). Contraindications to the use of TENS include pacemakers, epilepsy, and mental illness. TENS may be a useful option in the treatment of cancer pain, especially resistant to standard treatment and significantly reducing quality of life. It also has an analgesic effect on musculoskeletal and neuropathic pain [39]. Concerns regarding the safety and effect of TENS on cancer relate to the possible increased local blood supply to tissues due to electrical stimulation. However, the increased blood supply is due to muscle contraction; therefore, electrical stimulation below the motor threshold should not increase blood flow in a given body area.

Acupuncture

Acupuncture can be used to treat cancer pain, especially caused by tumors and surgery; analgesic effects are also possible in other pain syndromes that are difficult to treat, such as neuropathy after chemotherapy and joint pain induced by hormone therapy [40]. Clinical use of acupuncture in cancer patients may improve the effectiveness of standard pharmacotherapy in accordance with WHO recommendations and the quality of life of cancer patients [41].

Acupuncture is recommended by the American College of Chest Physicians for the treatment of pain in patients with lung cancer, especially when standard methods are ineffective or intolerable. Acupuncture is also recommended by the American Society of Clinical Oncology for the treatment of chronic pain in women during and after breast cancer therapy and in cancer survivors. Acupuncture is also recommended for elderly patients due to its effectiveness, low invasiveness, and significant safety [42].

Physical exercise

Many patients believe that rest and stillness can relieve pain. However, cancer patients can safely perform exercises both during and after cancer treatment. These exercises can reduce the intensity of anxiety, depression, and fatigue associated with cancer, as well as improve the quality of life and functioning of patients after anticancer treatment. The lower credibility of this evidence relates to beneficial effects of exercise on sleep quality. The exercise program should be selected individually according to the patient's preferences and performance status (PS) according to the Eastern Cooperative of Oncology Group (ECOG) scale. According to the recommendations, cancer patients with ECOG PS 0–2 can do moderate aerobic exercise (brisk walking, light cycling, water exercises) three times a week for 30 minutes and muscle strengthening exercises twice a week for 20–30 minutes. For patients with ECOG PS 3–4, programs individually selected by physiotherapists are recommended.

In elderly patients, in particular, moderate physical activity for a total of 150 minutes per week is recommended, but also shorter physical activities, such as slow walking and light housework. According to the WHO recommendations, elderly people with reduced mobility can perform physical activity 3 or more days a week to improve balance and prevent falls. When elderly people cannot perform the recommended physical activity due to their health condition, physical activity adapted to their capabilities is recommended [43].

Psychological support

Psychological methods used in the treatment of pain include meditation, hypnotherapy, relaxation, cognitive-behavioral therapy, biofeedback, visualization,

and music therapy [44]. The assumption is to influence various functions of the body through proper brain training. However, there are no studies evaluating the effectiveness of psychological methods in patients suffering from pain. The results of studies conducted in cancer patients indicate that psychological techniques can not only reduce the intensity of pain but also have a positive impact on other quality-of-life components, including reducing anxiety and improving the quality of sleep and mood [45]. In elderly cancer patients, psychoeducation methods are also effective, which include education about pain and its treatment, relaxation, training, and group support.

Interventional methods of pain management

Interventional methods include various techniques, from simple injections into tender points within the muscles to invasive neurodestructive methods and intrathecal implantation of catheters and stimulators (Tab. 5). The development of pharmacotherapy, and

Table 5. Therapeutic use of blockades/neurolysis/thermolesion/cryolesia

Type of pain	Blockades/neurolysis/ /thermolysis/cryolesia	Comment
I. Somatic pain:		
Myofascial	Trigger point blockades, injecting muscles and their fascia with LAs, peripheral nerve blocks	Technically simple, safe, and worth trying and propagating, it is advisable to monitor needle position under ultrasound guidance
Osteoarticular	Blockades of intervertebral and facet joints	Technically difficult, they require monitoring of needle/electrode position under the X-ray or US vision track
II. Visceral pain:		
Cancer-related	Stellate ganglion, plexuses: celiac, hypogastric superior The lumbar section of the sympathetic trunk, Walter's ganglion	Technically difficult, they require monitoring needle/electrode position under the X-ray or US vision track
Colicky pain	Epidural blockade in the lumbar or sacral region	Alternative/complement to systemic opioids
III. Vascular pain	Stellate ganglion, the lumbar section of the sympathetic trunk	The effect is very dependent on disease stage, high efficiency in rest pain, and requires monitoring the needle/electrode position under the X-ray or US vision track
IV. Neuropathic pain:		
Pancoast syndrome	Stellate ganglion, cervical epidural block, chordotomy	An alternative to ineffective pharmacotherapy of neuropathic pain, requires monitoring the needle/electrode position under the X-ray or US vision track Technically simple, effective in early stages of disease
Cranial nerve neuralgia	Blockades of peripheral branches of cranial nerves. Blockades of Gasser's ganglion, pterygopalatine ganglion. Gamma KNIFE/surgical decompression of neuro-vascular conflict	Technically difficult, high efficacy rate, monitoring the needle/electrode position under the X-ray or US vision track, in the case of Gamma KNIFE or surgical treatment it requires a neurosurgical center
PHN	Blockades of the sympathetic system. Epidural blockades	Technically difficult, requires monitoring the needle/electrode position under the X-ray or US vision track, effective up to 6 months from disease onset
Radiculopathies	Paravertebral blockades with LAs with addition of glucocorticosteroids	Effective in the acute disease phase
Stump pains	Blockades of trigger or tender points	Technically simple, the therapy of choice in early stages of disease, thermolesion/cryolesia requires monitoring the needle/electrode position under X-ray or ultrasound guidance
Phantom pains	Thermolesion/cryolesia of the stump Blockades of the sympathetic system	Technically difficult, require monitoring the needle/electrode position under the X-ray or US vision track

LA — local anesthetics; PHN — postherpetic neuralgia; US — ultrasonography

especially the introduction of many opioids and adjuvant analgesics, has significantly reduced the importance of interventional methods in recent years, although they are considered in 5–10% of patients. Interventional procedures in cancer patients should be considered at every stage of disease. The main indications for the use of interventional methods are pain that is resistant to pharmacological treatment, with a limited extent and clear localization, e.g., metastasis to the rib, compression of the intercostal nerve, or treatment-resistant side effects of pharmacotherapy [46]. Neurodestructive procedures can also be used in the early stages of the disease, especially neurolysis of the celiac plexus (II B) or the superior hypogastric plexus (II C) before the tumor causes significant anatomical distortions. Interventional methods of treatment should not be regarded as step IV of the WHO analgesic ladder but should be performed early enough when the patient begins to experience pain. This approach allows for a significant reduction in complex pharmacological treatment and/or delay in its initiation. The following minimally invasive intervention methods can be performed in cancer patients:

— blockade of tender trigger points in muscles;
— periarticular and intra-articular blockades;
— peripheral nerve, nerve plexus, and interfascial blocks.

In selected patients, more invasive interventional procedures can be performed in specialized units, such as:

— sympathetic blockades: celiac plexus, hypogastric plexus, Walther's ganglion;
— central blocks: epidural, subarachnoid;
— neurodestructive techniques: thermolesion, cryolesia, neurolysis, surgical procedures;
— intrathecal administration of drugs;
— invasive neuromodulation — stimulation of the spinal cord, peripheral nerves (Tab. 6).

Patients with multiple pain locations, a complex pain mechanism (central), dynamically intensifying pain, and poor general condition are carefully qualified for interventional methods. The patient's age is not a contraindication to the use of interventional methods.

The premise for the use of interventional techniques is the possibility of acting directly at the site of pain. An early and sometimes just one block may prevent the development of potential pain syndrome (phantom pain after limb/breast amputation, pain after thoracotomy/mastectomy). Blockades have a special role in pain syndromes, in which the modulating factor is the excessive activity of the sympathetic nervous system. A classic example of pain that may be dependent on the sympathetic nervous system is neuropathic pain, which occurs in 7–10% of the general population and in over 30% of cancer patients. Therefore, blocks are an important element of therapy for this type of pain [47]. Another possibility of using interventional techniques is their application to inject drugs into the immediate surroundings affected by the disease process: into joint and epidural space (opioids and steroids). In cancer patients, the positive effect of continuous epidural (II C) or subarachnoid (II B) blockade is especially related to neuropathic and bone pain, sometimes also inflammatory, by reducing swelling around the spinal cord.

Blockades are also used as an important diagnostic and prognostic method. A positive but short-term effect of a blockade may confirm the indication for neurodestructive surgery. In cancer patients, not only all advantages but also potential adverse effects of therapeutic treatment should be carefully considered. In each case of using interventional techniques, there is a risk of complications and side effects. Permanent damage to the nervous structures, especially the peripheral nerve, may be associated with unpleasant consequences, such as paresthesia, numbness, and motor deficits; therefore, before performing a neurodestructive procedure, patients should be informed about the possibility of side effects and potential complications. It is also necessary to obtain the patient's informed written consent for the procedure. Performing a neurodestructive procedure may be preceded by a diagnostic and prognostic block with the use of local anesthetics (LAs). This procedure helps to determine the source of pain and its mechanism and also indicates the patient the advantages and disadvantages of future neurolysis/thermolesion. It should be remembered that LAs are always stronger than neurodestructive agents, and the patient is exposed to the same procedure twice. It is always worth thinking carefully about performing a diagnostic block.

Elderly patients may be considered for an invasive procedure if they meet the following criteria:

— patient understands the purpose of the procedure and gives informed consent to the proposed procedure;
— the nature of pain corresponds to indications for use of a given method;
— safety aspects, e.g., use of anticoagulants, coagulation disorders, and local skin infection, are covered.

In cancer patients, one of the most frequently performed invasive procedures is neurolysis within the structures of the sympathetic nervous system:

— celiac plexus — in pain accompanying cancer of the pancreas, liver, and other organs in the epigastrium;
— the superior hypogastric plexus and ganglion impar (Walther) — in pain associated with pelvic tumors and in perineal pain.

Table 6. Most frequently performed interventional techniques in cancer patients

Interventional technique	Indications	Comment
Spinal/epidural neurolysis	Localized, unilateral, severe cancer pain, limited to 1–3 dermatomes, difficult to control with pharmacotherapy	Due to the properties gives a local anesthetic effect and hyperbaricity in relation to the cerebrospinal fluid; the preferred neurolytic agent is phenol Catheter insertion allows the administration of phenol in a fractionated manner, and the anesthetic properties of the drug allow for controlling blockade extent and improving procedure safety High risk of serious neurological complications (muscular weakness of lower limbs, damage to the sphincter function) The reason for incomplete effectiveness may be fibrosis in the spinal canal, e.g., after radiotherapy, which isolates the nerve roots from the administered drug
Neurolysis/ /thermolesion/ /cryolesia of peripheral nerves: intercostal, suprascapular, occipital, intercostobrachial	Cancer pain due to rib metastases or chest wall invasion, chest wall pain syndromes, pain after mastectomy/thoracotomy Painful shoulder syndrome, bone pain resulting from metastases to the scapula, shoulder joint, or humerus Suprascapular neuralgia, occipital neuralgia, headaches: tension, Horton's migraine, post-puncture Intercostobrachial neuralgia after mastectomy	Simple techniques, however, require ultrasound-guided monitoring of the needle/electrode position to reduce the risk of complications (hematoma/intravascular administration/pneumothorax in the case of intercostal blockage) Due to the overlap of dermatomes, two adjacent intercostal spaces must be destroyed to achieve a good intercostal block effect Intercostal nerve neurolysis has been completely replaced by the thermolesion/cryolesia technique
Intrapleural neurolysis	Pleural and chest wall pain due to lung, breast, kidney, and pancreatic tumors	Simple blockade technique, identical to intrapleural LA blockade based on loss of resistance technique Insertion of the needle above the upper rib edge in a lateral position in the mid-scapular line
Neurolysis/ /thermolesion/ /cryolesia of the pterygopalatine ganglion, thermolesion of Gasser's ganglion	Neuralgia, trigeminal neuropathy, atypical facial pain, trigeminal autonomic headache, migraine, post-puncture headache, PHN of 1 branch of the trigeminal nerve, facial pain due to craniofacial tumors	Technically difficult due to significant variability of the anatomical structure of the facial skeleton They require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm and contrast administration, which in pterygopalatine ganglion block should be placed in points against maxillary sinus background, and in Gasser's ganglion block, monitoring under the X-ray vision track helps to localize the foramen ovale Side effects in pterygopalatine ganglion blockade result from technical errors and incorrect depositing of the neurolytic agent: corneal ulceration (agent infiltration into the orbit), facial nerve palsy (agent infiltration into the styloid process)
Neurolysis/ /thermolesion/ /cryolesia of stellate ganglion	Upper limb vascular pain, pain after thoracotomy and mastectomy, phantom pain, lymphedema pain, PHN, Pancoast syndrome, CRPS	Neurolysis has been replaced by the thermolesion/cryolesia technique Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm and contrast administration Complications: intravascular or intrathecal administration with generalized toxic reaction/total spinal anesthesia, pneumothorax, recurrent laryngeal, and phrenic nerve palsy, Horner's syndrome
Celiac plexus neurolysis	Cancer-related visceral pain in the upper abdominal cavity (cancer of the pancreatic head, stomach, gallbladder, liver), CP	Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C-arm, TC-arm in the transdiaphragmatic peri- or transaortic approach or ultrasound in the anterior approach and contrast administration, which should be placed linearly on the anterior wall of the abdominal aorta at Th12 level It causes a high sympathetic blockade; therefore, it requires prophylaxis of blood pressure drop

→

Table 6 cont. Most frequently performed interventional techniques in cancer patients

Interventional technique	Indications	Comment
		High (70–85%) effectiveness in the treatment of visceral pain for pancreatic head cancer (II A)
		Ineffective in cancers of the pancreatic body and tail due to the large size of tumors located in this area, which prevents good coverage of the celiac plexus with a neurolytic agent
Thermolesion of visceral nerves at Th11 level	As above	Technically difficult, require experience and monitoring of the needle/electrode position under the X-ray vision track with the C- or TC-arm
Celiac plexus radioablation	As above	Technically difficult, requires experience to select an ionizing radiation dose that is safe for organs
Bilateral thoracoscopic splanchnicectomy	Cancer-related visceral pain in the course of the pancreatic body and tail, CP	Bilateral transection of visceral nerves under visual control should be performed by an experienced endoscopic surgeon
		The procedure requires the patient's prone position so that the surgeon has free access to both pleural cavities without the need to change the patient's position during the procedure and intubation with a double-lumen tube (DLT) and alternate deflation of both lungs
		With no risk of serious complications, including neurological ones associated with classic neurolysis of visceral nerves
		Effective in large pancreatic tumors
Neurolysis of the lumbar section of the sympathetic trunk	Pain in the lower abdomen and lower limbs dependent on the sympathetic system: vascular, neuropathic (CRPS, PHN, FBSS, phantom), cancer, post-traumatic, degenerative pain	Technically easy, but requires monitoring the correct position of the needles using X-ray vision track with C-arm and contrast administration, which should be placed linearly along the iliopsoas muscle
		Due to the considerable length of the lumbar section of the sympathetic trunk, the technique with use of two needles inserted at L2 and L4 levels is recommended
Neurolysis of superior hypogastric plexus	Visceral pain in the course of pelvic cancer: uterus, prostate, rectum, bladder	Technically very difficult, requires a lot of experience and monitoring the correct position of the needle using X-ray vision track with C-arm (two AP and lateral projections are necessary to ensure that the contrast and then the neurolytic agent are administered to the anterior surface of L5–S1 vertebral bodies)
Neurolysis of Walter's ganglion	Cancer pain in the perineal and anal area, phantom pain after rectal resection, perineal pain in the course of pelvic pain syndrome	Technically easy, requires monitoring the correct position of the needle tip using the X-ray vision track and contrast administration or ultrasound
		The sacrococcygeal area can be reached with a bent needle or via the sacrococcygeal junction
Drugs administered intrathecally	Cancer pain resistant to treatment or intolerable side effects of pharmacotherapy, inability to use other interventional methods	About 2% of patients with cancer pain require the use of intrathecal drugs (LAs, opioids, corticosteroids, ketamine, baclofen, magnesium, ziconotide)
		An epidural or subarachnoid catheter is connected to an external or implantable pump
		Contraindications: infection at the puncture site, coagulation disorders, tumor in the spinal canal, anticipated difficulties in pump operation
Vertebroplasty/ /kyphoplasty	Metastases to the vertebral body, pathological or osteoporotic fracture	Bone cement injection to stabilize the vertebral body
		An experienced orthopedist or a neurosurgeon should perform the procedure
		It effectively relieves pain with a relatively low complication rate and an acceptable benefit/risk ratio

AP — anterior-posterior; CP — chronic pancreatitis; CRPS — complex regional pain syndrome; FBSS — frontal behavioral spatial complex; LA — local anesthetics; PHN — postherpetic neuralgia

Neurodestructive procedures can be conducted by physical or chemical factors or surgical incisions (mechanical factors). The physical factors that damage nerve fibers include low (cryolesia) and high temperature (thermolesion) and hypo- and hyperosmotic solutions. Chemical agents that damage nerve fibers include

primarily ethyl alcohol and, less often, phenol and glycerol. Nervous tissue, such as the celiac plexus, can also be damaged by ionizing radiation (radioablation of the celiac plexus), which consists of the destruction of the celiac plexus and pancreatic tumor with a safe dose of ionizing radiation. The procedure is used in patients with pancreatic neoplasms, in whom neurolysis of the celiac plexus cannot be performed (due to too large tumor dimensions, especially located within the body and tail of the pancreas, or vascular infiltration). It is one of the most modern interventional techniques used in the treatment of pain in patients with pancreatic cancer. Poland was the first country in Europe where such procedures were performed [48].

The neurodestructive mechanism of a chemical compound with a neurolytic effect includes inducing Wallerian degeneration of nerve fibers, i.e., the disintegration of protein and lipid substances in axons and changes in myelin sheaths. The increase in fluid pressure inside the nerve fiber impairs blood flow in the blood vessels supplying the nerve. Shortly after the destruction of nerve structures, the regeneration process begins, the duration of which depends on the extent of neurodestruction — usually, the nerve fiber regenerates at a rate of about 1 mm/day. The drug is administered near the nerve without affecting its structure.

Ethyl alcohol is the oldest and most commonly used neurolytic agent with low toxicity, used in a concentration of 50–100% (usually about 65%). Alcoholic neurolysis occurs rapidly and lasts for 5–7 months. Factors limiting the use of alcohol include rapid tissue diffusion, which requires the use of large volumes, making it more difficult to obtain a spatially limited neurolytic effect. During alcohol injection, the patient may experience pain, and alcoholic neuritis may occur. Tissue irritation caused by alcohol can be reduced by using a mixture with LAs, the alcohol concentration is then about 65%; it is also beneficial to rinse the needle with 1–2 mL of 0.9% NaCl or lignocaine. Accidental entry of alcohol into the tissues can cause local neuralgia.

In clinical practice, neurodestructive procedures within sympathetic fibers and/or ganglia, neurodestruction of the sensory roots of the spinal cord, and, selectively, mixed nerves are mainly performed [49]. The most commonly performed celiac plexus neurolysis reduces the intensity of pain in 90% of patients with pancreatic cancer, while complete pain relief is reported by up to 60% of patients. Neurolysis allows reducing the dose of systemically administered opioids, but it does not completely replace pharmacological treatment. An alternative to celiac plexus neurolysis may be celiac nerve neurolysis/thermolesion. The most common use of blockades and neurolysis in cancer patients is presented in Tables 4 and 5. Interventional methods of pain treatment may be associated with serious complications; therefore, they should be performed in specialized units after a thorough analysis of indications and contraindications [50].

Conclusions

In order to obtain the optimal effect of analgesic therapy, cancer patients require a comprehensive clinical assessment of pain, with the recognition of the pathophysiology, intensity, time pattern of pain, other symptoms, comorbidities, and disturbances in the psychological, social and spiritual dimension that may contribute to the patient's suffering and occurrence of total pain. The standard treatment is based on the WHO analgesic ladder algorithm and individualization of pain therapy, depending on the patient's clinical situation, taking into account non-pharmacological methods. Efforts should also be made to ensure effective treatment of other symptoms associated with cancer. Palliative and supportive care improves the quality of life of cancer patients by increasing overall survival and improving the quality of life for families and caregivers. The basic principles of pain pharmacotherapy in cancer patients include:

— oral and transdermal administration of analgesics, if possible and acceptable by patients;
— administration of analgesics at regular intervals and rescue agents in episodes of pain intensification (breakthrough, episodic pain);
— the choice of an analgesic depends mainly on pain intensity assessed by patients;
— drug dosage is selected individually: the optimal dose provides effective analgesia with acceptable side effects;
— attention to detail, monitoring of analgesic effectiveness, side effects, and quality of life of patients and families.

Article Information and Declarations

Funding

The article was not funded.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

References

1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020; 161(9): 1976–1982, doi: 10.1097/j.pain.0000000000001939, indexed in Pubmed: 32694387.
2. Higginson IJ, Murtagh F. Cancer pain epidemiology. In: Bruera E, Portenoy RK. ed. Cancer Pain. Assessment and Management. Cambridge University Press 2010: 37–52.
3. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. Ann Oncol. 2009; 20(8): 1420–1433, doi: 10.1093/annonc/mdp001, indexed in Pubmed: 19244085.
4. van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. Ann Oncol. 2007; 18(9): 1437–1449, doi: 10.1093/annonc/mdm056, indexed in Pubmed: 17355955.
5. De Walden–Gałuszko K, Majkowicz M. Psychologiczno–kliniczna ocena bólu przewlekłego. Wskazania dla lekarzy pierwszego kontaktu oraz poradni przeciwbólowych i paliatywnych. Akademia Medyczna, Gdańsk 2003.
6. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005; 114(1-2): 29–36, doi: 10.1016/j.pain.2004.12.010, indexed in Pubmed: 15733628.
7. Turczyn P, Kosińska B, Janikowska-Hołoweńko D, et al. Translation and cross-cultural adaptation of the Polish Central Sensitization Inventory. Reumatologia. 2019; 57(3): 129–134, doi: 10.5114/reum.2019.86422, indexed in Pubmed: 31462827.
8. https://opiekunrodzinny.pl/jestem-opiekunem/opiekuje-sie-chorym-doroslym/opieka-nad-chorym-porady/skuteczne-leczenie-bolu/leczenie-bolu-w-praktyce/ (21.04.2023).
9. den Boer C, Dries L, Terluin B, et al. Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments. J Psychosom Res. 2019; 117: 32–40, doi: 10.1016/j.jpsychores.2018.12.010, indexed in Pubmed: 30665594.
10. Løhre ET, Klepstad P, Bennett MI, et al. European Association for Palliative Care Research Network. From „Breakthrough" to „Episodic" Cancer Pain? A European Association for Palliative Care Research Network Expert Delphi Survey Toward a Common Terminology and Classification of Transient Cancer Pain Exacerbations. J Pain Symptom Manage. 2016; 51(6): 1013–1019, doi: 10.1016/j.jpainsymman.2015.12.329, indexed in Pubmed: 26921493.
11. Mercadante S, Radbruch L, Caraceni A, et al. Steering Committee of the European Association for Palliative Care (EAPC) Research Network. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. Cancer. 2002; 94(3): 832–839, doi: 10.1002/cncr.10249, indexed in Pubmed: 11857319.
12. Leppert W, Forycka M, Nosek K. Breakthrough and episodic pain in cancer patients – a new look. Med Paliat. 2016; 8(1): 9–16.
13. Caraceni A, Hanks G, Kaasa S, et al. European Palliative Care Research Collaborative (EPCRC), European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012; 13(2): e58–e68, doi: 10.1016/S1470-2045(12)70040-2, indexed in Pubmed: 22300860.
14. Fallon M, Giusti R, Aielli F, et al. ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018; 29(Suppl 4): iv166–iv191, doi: 10.1093/annonc/mdy152, indexed in Pubmed: 30052758.
15. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents 2018.
16. Bennett MI, Eisenberg E, Ahmedzai SH, et al. Standards for the management of cancer-related pain across Europe-A position paper from the EFIC Task Force on Cancer Pain. Eur J Pain. 2019; 23(4): 660–668, doi: 10.1002/ejp.1346, indexed in Pubmed: 30480345.
17. Paice JA, Bohlke K, Barton D, et al. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. J Clin Oncol. 2023; 41(4): 914–930, doi: 10.1200/JCO.22.02198, indexed in Pubmed: 36469839.
18. Corli O, Floriani I, Roberto A, et al. CERP STUDY OF PAIN GROUP (List of collaborators). Are strong opioids equally effective and safe in the treatment of chronic cancer pain? A multicenter randomized phase IV ‚real life' trial on the variability of response to opioids. Ann Oncol. 2016; 27(6): 1107–1115, doi: 10.1093/annonc/mdw097, indexed in Pubmed: 26940689.
19. Reid CM, Gooberman-Hill R, Hanks GW. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. Ann Oncol. 2008; 19(1): 44–48, doi: 10.1093/annonc/mdm462, indexed in Pubmed: 18073222.
20. De Conno F, Ripamonti C, Fagnoni E, et al. MERITO Study Group. The MERITO Study: a multicentre trial of the analgesic effect and tolerability of normal-release oral morphine during ‚titration phase' in patients with cancer pain. Palliat Med. 2008; 22(3): 214–221, doi: 10.1177/0269216308088692, indexed in Pubmed: 18477715.
21. Bandieri E, Romero M, Ripamonti CI, et al. Early Strong Opioid Treatment Study (ESOT) Investigators. Randomized Trial of Low-Dose Morphine Versus Weak Opioids in Moderate Cancer Pain. J Clin Oncol. 2016; 34(5): 436–442, doi: 10.1200/JCO.2015.61.0733, indexed in Pubmed: 26644526.
22. Riley J, Branford R, Droney J, et al. Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. J Pain Symptom Manage. 2015; 49(2): 161–172, doi: 10.1016/j.jpainsymman.2014.05.021, indexed in Pubmed: 24975432.
23. Zecca E, Brunelli C, Bracchi P, et al. Comparison of the Tolerability Profile of Controlled-Release Oral Morphine and Oxycodone for Cancer Pain Treatment. An Open-Label Randomized Controlled Trial. J Pain Symptom Manage. 2016; 52(6): 783–794.e6, doi: 10.1016/j.jpainsymman.2016.05.030, indexed in Pubmed: 27742577.
24. Ahmedzai SH, Nauck F, Bar-Sela G, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med. 2012; 26(1): 50–60, doi: 10.1177/0269216311418869, indexed in Pubmed: 21937568.
25. Ahmedzai SH, Leppert W, Janecki M, et al. Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain. Support Care Cancer. 2015; 23(3): 823–830, doi: 10.1007/s00520-014-2435-5, indexed in Pubmed: 25218610.
26. Wang DD, Ma TT, Zhu HD, et al. Transdermal fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. J Cancer Res Ther. 2018; 14(Supplement): S14–S21, doi: 10.4103/0973-1482.171368, indexed in Pubmed: 29578144.
27. Zeppetella G, Davies A, Eijgelshoven I, et al. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. J Pain Symptom Manage. 2014; 47(4): 772–785.e5, doi: 10.1016/j.jpainsymman.2013.05.020, indexed in Pubmed: 23981487.
28. Cachia E, Ahmedzai SH. Transdermal opioids for cancer pain. Curr Opin Support Palliat Care. 2011; 5(1): 15–19, doi: 10.1097/SPC.0b013e3283437a39, indexed in Pubmed: 21325999.
29. Schmidt-Hansen M, Bromham N, Taubert M, et al. Buprenorphine for treating cancer pain. Cochrane Database Syst Rev. 2015; 2015(3): CD009596, doi: 10.1002/14651858.CD009596.pub4, indexed in Pubmed: 25826743.
30. Zajączkowska R, Przewłocka B, Kocot-Kępska M, et al. Tapentadol - A representative of a new class of MOR-NRI analgesics. Pharmacol Rep. 2018; 70(4): 812–820, doi: 10.1016/j.pharep.2018.01.005, indexed in Pubmed: 29921501.
31. Wiffen PJ, Derry S, Naessens K, et al. Oral tapentadol for cancer pain. Cochrane Database Syst Rev. 2015; 2015(9): CD011460, doi: 10.1002/14651858.CD011460.pub2, indexed in Pubmed: 26403220.
32. Nicholson AB, Watson GR, Derry S, et al. Methadone for cancer pain. Cochrane Database Syst Rev. 2017; 2(2): CD003971, doi: 10.1002/14651858.CD003971.pub4, indexed in Pubmed: 28177515.
33. Wiffen PJ, Wee B, Derry S, et al. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017; 7(7): CD012592, doi: 10.1002/14651858.CD012592.pub2, indexed in Pubmed: 28683172.
34. Wordliczek J, Kotlińska-Lemieszek A, Leppert W, et al. Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. Pol Przegl Chir. 2018; 90(4): 55–84, doi: 10.5604/01.3001.0012.2904, indexed in Pubmed: 30293970.
35. Leppert W, Wordliczek J. Recommendations for assessment and management of pain in cancer patients. Oncol Clin Pract. 2018; 14(1): 1–14, doi: 10.5603/OCP.2018.0005.
36. Kalso E. Clinical pharmacology of opioids in the treatment of pain. In: Mogil J. ed. Pain 2010 – An Updated Review. IASP Press, Seattle 2010: 207–216.
37. Ruano A, García-Torres F, Gálvez-Lara M, et al. Psychological and Non-Pharmacologic Treatments for Pain in Cancer Patients: A Sys-

tematic Review and Meta-Analysis. J Pain Symptom Manage. 2022; 63(5): e505–e520, doi: 10.1016/j.jpainsymman.2021.12.021, indexed in Pubmed: 34952171.
38. Pyszora A, Jagielski D, Jagielska A. Physiotherapy for mysofascial pain syndrome in cancer patient. Med Paliat Prakt. 2015; 9(2): 55–58.
39. Hurlow A, Bennett MI, Robb KA, et al. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. Cochrane Database Syst Rev. 2012; 2012(3): CD006276, doi: 10.1002/14651858.CD006276.pub3, indexed in Pubmed: 22419313.
40. Paley CA, Johnson MI, Tashani OA, et al. Acupuncture for cancer pain in adults. Cochrane Database Syst Rev. 2015; 2015(10): CD007753, doi: 10.1002/14651858.CD007753.pub3, indexed in Pubmed: 26468973.
41. He Y, Guo X, May BH, et al. Clinical Evidence for Association of Acupuncture and Acupressure With Improved Cancer Pain: A Systematic Review and Meta-Analysis. JAMA Oncol. 2020; 6(2): 271–278, doi: 10.1001/jamaoncol.2019.5233, indexed in Pubmed: 31855257.
42. Yang J, Wahner-Roedler DL, Zhou X, et al. Acupuncture for palliative cancer pain management: systematic review. BMJ Support Palliat Care. 2021; 11(3): 264–270, doi: 10.1136/bmjspcare-2020-002638, indexed in Pubmed: 33441387.
43. Kocot–Kępska M, Mitka K, Rybicka M, et al. The role of physical activity in cancer patients: a narrative review. Palliat Med Pract. 2021; 15(3): 254–262.
44. Warth M, Zöller J, Köhler F, et al. Psychosocial Interventions for Pain Management in Advanced Cancer Patients: a Systematic Review and Meta-analysis. Curr Oncol Rep. 2020; 22(1): 3, doi: 10.1007/s11912-020-0870-7, indexed in Pubmed: 31965361.
45. Braunwalder C, Müller R, Glisic M, et al. Are Positive Psychology Interventions Efficacious in Chronic Pain Treatment? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Med. 2022; 23(1): 122–136, doi: 10.1093/pm/pnab247, indexed in Pubmed: 34347095.
46. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010; 85(3 Suppl): S3–14, doi: 10.4065/mcp.2009.0649, indexed in Pubmed: 20194146.
47. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015; 14(2): 162–173, doi: 10.1016/S1474-4422(14)70251-0, indexed in Pubmed: 25575710.
48. Miszczyk M, Wydmański J, Kocot-Kępska M, et al. Noninvasive celiac plexus radiosurgery in palliative treatment for patients with symptomatic pancreatic cancer. Contemp Oncol (Pozn). 2021; 25(2): 140–145, doi: 10.5114/wo.2021.107689, indexed in Pubmed: 34667441.
49. Garg R, Joshi S, Mishra S, et al. Evidence based practice of chronic pain. Indian J Palliat Care. 2012; 18(3): 155–161, doi: 10.4103/0973-1075.105684, indexed in Pubmed: 23439674.
50. Bhatnagar S, Gupta M. Evidence-based Clinical Practice Guidelines for Interventional Pain Management in Cancer Pain. Indian J Palliat Care. 2015; 21(2): 137–147, doi: 10.4103/0973-1075.156466, indexed in Pubmed: 26009665.

Joanna Kufel-Grabowska[1], Krzysztof Łukaszuk[2, 3], Magdalena Błażek[4], Agnieszka Jagiełło-Gruszfeld[5], Anna Horbaczewska[6, 7], Ninela Irga-Jaworska[8], Robert Jach[6, 7], Piotr Jędrzejczak[9, 10], Izabela Kopeć[11], Maryna Krawczuk-Rybak[12], Maciej Krzakowski[13], Katarzyna Pogoda[5], Maria Sąsiadek[14], Robert Spaczyński[10], Monika Urbaniak[15], Elżbieta Wojciechowska-Lampka[16], Sławomir Wołczyński[17], Jacek Jassem[1]

[1]Department and Clinic of Oncology and Radiotherapy, Medical University of Gdańsk, Poland
[2]Department of Obstetrics and Gynecology Nursing, Medical University of Gdańsk, Poland
[3]Invicta — Fertility Clinics in Gdańsk, Poland
[4]Department of Psychology, Department of Quality of Life Research, Medical University of Gdańsk, Poland
[5]Department of Breast Cancer and Reconstructive Surgery, National Oncology Institute of Maria Sklodowska-Curie — National Research Institute, Warsaw, Poland
[6]Department of Gynecology and Obstetrics, Jagiellonian University, Krakow, Poland
[7]Department of Gynecological Endocrinology and Gynecology, University Hospital, Krakow, Poland
[8]Department and Clinic of Pediatrics, Hematology and Oncology, Medical University of Gdańsk, Poland
[9]Department of Cell Biology, Poznan University of Medical Sciences, Poland
[10]Center of Gynecology, Obstetrics and Infertility Treatment Pastelova, Poznań, Poland
[11]Hematology Clinic for Pregnant Women, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[12]Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Poland
[13]Department of Lung and Chest Cancer, National Oncology Institute of Maria Sklodowska-Curie — National Research Institute, Warsaw, Poland
[14]Department and Department of Genetics, Medical University of Wrocław, Poland
[15]Chair and Department of Medical and Pharmaceutical Law, Poznan University of Medical Sciences, Poland
[16]Department of Lymphoid Malignancies, National Oncology Institute of Maria Sklodowska-Curie — National Research Institute, Warsaw, Poland
[17]Department of Reproductive and Gynecological Endocrinology, Medical University of Bialystok, Poland

Fertility preservation during oncological treatment

1. *Quality of evidence:*
   I — Evidence obtained from properly designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Evidence obtained from properly designed and conducted prospective observational studies (non-randomized cohort studies)
   III — Evidence obtained from retrospective, observational, or case-control studies
   IV — Evidence obtained from experience gained in clinical practice and/or expert opinions
2. *Recommendation categories:*
   A — Indications confirmed unequivocally and extremely useful in clinical practice
   B — Indications likely to be potentially useful in clinical practice
   C — Indications defined individually

Introduction

The number of new cancer cases is increasing worldwide. Early diagnosis of cancer and appropriate therapy improve prognosis. One of the more serious effects of oncological treatment is the impairment of reproductive functions, leading to temporary or permanent infertility. Fertility protection in children and adults of reproductive age receiving oncological treatment is part of standard oncological care.

Received: 14.04.2023 Accepted: 26.05.2023 Early publication date: 04.08.2023

Address for correspondence: Joanna Kufel-Grabowska, MD PhD, Department and Clinic of Oncology and Radiotherapy, Medical University of Gdańsk, ul. Marii Skłodowskiej-Curie 3a, 80–210 Gdańsk, Poland, e-mail: joanna.kufel-grabowska@gumed.edu.pl

Translation: dr n. med. Dariusz Stencel
Oncol Clin Pract 2024, Vol. 20, No. 2, 100–116, DOI: 10.5603/OCP.2023.0033, Copyright © 2024 Via Medica, ISSN 2450–1654, e-ISSN 2450–6478

Genetic basis of cancer in children and people of reproductive age

According to the data from the National Cancer Registry, 146 200 new cancer cases and 99 900 cancer-related deaths were registered in 2020 [1]. Cancer transformation is driven by abnormalities in genetic information, leading to acquisition of new, specific biological cell features [2, 3]. The first critical genetic abnormality can occur in any cell of the body and initiate neoplastic transformation in a specific location. These sporadic, non-hereditary changes account for about 75% of all cancers. If the abnormality occurs in the reproductive cells, it will be passed on to subsequent generations, leading to a hereditary cancer risk syndrome. Hereditary mutations affect 5–10% of all cancers [4, 5]. Most often, these abnormalities are inherited as autosomal dominants, rarely autosomal recessives. Identification of the hereditary burden of increased cancer risk syndrome improves medical care and allows taking preventive measures for the affected person and their family members [6]. On this basis, information should also be provided about the risk of passing a critical mutation to offspring and about possibilities of reducing this risk [7].

Recommendations

1. Access to clinical genetics consultation should be provided to any person suspected of having a hereditary cancer risk syndrome (IV, A).
2. Each carrier of a hereditary mutation (child and adult) with increased risk of cancer development should receive oral and written information about the risk of passing a critical mutation to offspring and the possibilities of reducing it by *in vitro* fertilization with genetic preimplantation diagnostics (IV, A).

Fertility counseling

All cancer patients of reproductive age, regardless of sex, cancer type and stage, should have access to fertility counseling before starting oncological treatment and preferably immediately after a cancer diagnosis.

The conversation with the patient and possibly his/her partner should take into account the patient's situation, procreative plans, having a partner, and possible genetic predisposition. Patients should be provided with information on the possibility of preserving fertility, the optimal time to try to conceive, course of pregnancy, and impact of oncological treatment on future offspring. Counseling should also be offered to patients who, at the time of diagnosis, do not plan to have children in the future. Individual management is determined by an interdisciplinary team consisting of an oncologist, a specialist in reproductive medicine, and a psychologist [8, 9].

Recommendations

1. Every cancer patient of reproductive age, regardless of sex, cancer type, and stage, should be informed about the risk of reproductive impairment before starting oncological treatment and should receive advice from a reproductive medicine specialist on how to reduce this risk (III, A).
2. Counseling about fertility preservation should take into account the patient's situation, sex and gender, age, cancer type and stage, type of planned treatment, possible genetic burden, and procreation plans (III, A).
3. Information on fertility preservation should be provided to the patient orally and in writing, and his/her decision should be documented in the medical records (IV, A).

Gonadotoxicity of oncological treatment

The gonadotoxic effect of standard anticancer treatment in men and women is quite well understood. Less is known about the risks associated with new treatments.

Surgery

Surgical treatment of women

Surgical procedures in the treatment of gynecological cancers have a direct impact on female reproductive potential [10–12]. The only way to have children after hysterectomy is to use surrogacy, but this method is not legally available in Poland.

Fertility-sparing treatment for ovarian cancer and borderline ovarian tumors

Fertility preservation involving unilateral adnexectomy while preserving the uterus is possible in patients with stage IA or IC1, low-grade serous, endometrial, or mucinous ovarian cancer (OC) with expanding growth [13].

Uterine preservation with unilateral adnexectomy may also be considered in selected, younger patients with stage IB OC with low risk of invasion and normal endometrial biopsy; however, data on this approach are scarce. In borderline tumors and stage IA mucinous carcinoma, unilateral oophorectomy is performed. In stage IB, when tumors occur in both ovaries, enucleation of the tumor from one or even both ovaries may be considered [14].

Fertility-sparing treatment for endometrial cancer

Fertility-sparing treatment may be used in patients with atypical hyperplasia/intraepithelial neoplasia of the endometrium or endometrial cancer grade G1. In these patients, uterine curettage or hysteroscopic

endometrial biopsy should be performed and medroxyprogesterone acetate (400–600 mg/day) or megestrol acetate (160–320 mg/day) should be used. Treatment with a levonorgestrel-releasing intrauterine device (IUD) with or without gonadotropin-releasing hormone analogs may also be considered. After 6 months, curettage of the uterine cavity, hysteroscopy, and imaging should be performed. No response to treatment is an indication for standard surgery. In the case of a complete response, the patient can try to become pregnant. Maintenance therapy should be considered in responding patients who wish to delay pregnancy. If hysterectomy has not been performed, a clinical evaluation should be performed every 6 months. After the patient has ended her procreation plans, it is recommended to perform a hysterectomy with removal of the ovaries and fallopian tubes (Salpingo-oophorectomy); ovarian sparing is debatable [15].

Fertility-sparing treatment for cervical cancer

Fertility-sparing treatment can be used in patients with squamous cell cervical carcinoma or adenocarcinoma up to 2 cm in size. It is not recommended in rare more malignant histological subtypes, for example, neuroendocrine tumors and adenocarcinomas unrelated to human papillomavirus (HPV) infection. If this procedure is planned, the first step should be the evaluation of the sentinel node. Patients with T1a1 and T1a2 N0 stages can undergo conization and simple trachelectomy. Radical trachelectomy (type A) may be considered at stages T1a1 and T1a2 N0 with vascular infiltration. Radical trachelectomy (type B) should be performed at stage T1b1 N0 with a lesion ≤ 2 cm and infiltration of the vascular spaces. There is no need for routine hysterectomy after the termination of reproductive plans [16].

Surgical treatment of men

Unilateral orchidectomy is routinely used as the first step in the treatment of primary testicular cancers. Resection of retroperitoneal lymph nodes, prostatectomy, cystectomy, pelvic exenteration, resection of the lower anterior colon, or any similar deep pelvic surgery may damage the vas deferens, ejaculatory duct, or seminal vesicles, which together form the testicular duct system. These procedures may also cause damage to the cavernous nerve with erectile dysfunction, damage to the autonomic nerves with impaired ejaculation, and physical interruption or obstruction of the seminal tract, as well as erectile dysfunction and/or dysfunction of the autonomic nerves [17].

Recommendations

1. All women of childbearing potential starting treatment should undergo individual fertility risk assessment by a multidisciplinary team (IV, A).
2. Fertility-preserving surgery may be considered in patients with stage IA or IC1, low-grade serous, endometrial, or mucinous ovarian cancer with expanding growth (III, C).
3. Fertility-sparing treatment may be used in patients with atypical hyperplasia/intraepithelial neoplasia of the endometrium or endometrial cancer of grade G1 (III, C).
4. Fertility-preserving treatment may be considered in patients with HPV-related cervical squamous cell carcinoma or adenocarcinoma up to 2 cm in size with negative margins and N0 disease (III, C).
5. Sperm cryopreservation should be considered before any testicular or other pelvic surgery (III, A).

Radiotherapy

Reproductive cells are particularly sensitive to ionizing radiation. Even small doses of radiotherapy reduce the number of male and female reproductive cells and may cause mutagenic changes. The damaging effect depends on the initial germ cell quality, irradiation dose, fractionation, and irradiated area (Tab. 1). A dose > 0.2 Gy affecting the gonads impairs spermatogenesis, and > 4 Gy causes irreversible changes. At doses of 1 to 2 Gy, spermatogenesis can be expected to return to a normal level after about 1 to 3.5 years [18]. A single dose is more gonadotoxic than several smaller fractions [19]. Irradiation of retroperitoneal lymph nodes results in dispersion of part of the dose to the vicinity of testicles, which justifies shielding them [20].

Administration of a dose of 2 Gy to the ovaries accelerates follicular atresia and reduces their pool. At the age of 15, a dose of 16 Gy causes permanent sterilization, and at the age of 30, it is 12 Gy. Radiotherapy of the pelvic area leads to abnormal development, growth, and trophic disorders of the uterus, vagina, and ovaries [21]. Irradiation also affects the elasticity of the uterus, which can lead to an abnormal course of pregnancy (miscarriage, abnormal placental development, premature birth, or uterine rupture), and in girls, it can cause abnormal development of the uterus.

In the case of total body irradiation (TBI) before hematopoietic stem cell transplantation, the risk of premature ovarian and testicular failure reaches 90% and is irreversible in most cases [22].

Central nervous system irradiation may cause secondary hypogonadism; doses of 30–40 Gy lead to secondary ovarian and testicular failure in 80% of patients. Damage to pituitary cells can be a significant cause of abnormal secretion of growth hormones, sex hormones, and adrenal and thyroid hormones. The consequence of brain irradiation may also be hyperprolactinemia caused by a deficiency of the inhibitory neurotransmitter dopamine. It affects 20–50% of women

Table 1. Risk of gonadotoxicity after radiotherapy in women depending on dose and age

Total dose and irradiation area	Risk of gonadotoxicity in the prepubertal period	Risk of gonadotoxicity in women aged 15–40 years	Risk of gonadotoxicity in women > 40 years of age
< 6 Gy per abdomen/pelvis	Moderate	None	None
15 Gy per abdomen/pelvis	High	Low	Moderate
25–50 Gy per abdomen/pelvis	High	Moderate	High
50–80 Gy per abdomen/pelvis	High	Moderate	High
CNS and spinal cord irradiation	Moderate	Moderate	Moderate
Whole body irradiation	High	High	High

CNS — central nervous system

and about 5% of children and is usually asymptomatic [23–24].

Irradiation of the thyroid area may cause hormonal disorders, disrupting the menstrual cycle.

Recommendations

1. Irrespective of the planned dose of radiotherapy to the testicular area, semen preservation is recommended before it starts (III, A).
2. In patients irradiated to the pelvic area, a testicular shield should be used (III, A).
3. In women of childbearing potential, ovarian transposition and freezing of oocytes, embryos, or ovarian fragments should be considered before starting radiotherapy (III, A).
4. In patients receiving whole-body irradiation, one of the available methods of fertility protection should be considered (III, A).
5. Due to the risk of secondary hypogonadism, it is advisable to use one of the available methods of fertility protection before starting brain irradiation (III, A).

Chemotherapy

Cytotoxic drugs can damage gonadal function and reduce fertility in children and people of reproductive age [25–28]. Chemotherapy-induced fertility disorders in women are most often manifested by amenorrhea at various times after its completion, possibly in combination with postmenopausal hormone levels [27].

In breast cancer, amenorrhea occurs in approximately 80% of patients receiving the combination of docetaxel and cyclophosphamide or doxorubicin and cyclophosphamide followed by a taxoid. At the same time, there is a deep and long-term decrease in anti-Mullerian hormone (AMH) levels [29, 30]. Dose-dense chemotherapy regimens used in breast cancer patients do not increase the risk of amenorrhea compared to the standard regimen [31].

In Hodgkin lymphoma, premature ovarian failure due to chemotherapy occurs in about 40% of women. In women aged 15–40, the cumulative risk of premature ovarian failure after treatment with and without alkylating drugs is 60% and 3–6%, respectively [32]. In patients with non-Hodgkin's lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOPE3 (CHOP + etoposide) regimens, earlier menopause and lower AMH levels were found [33]. Azoospermia, sometimes causing permanent infertility, has been observed in more than 90% of patients treated with procarbazine [34]. ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) is less gonadotoxic [35].

In patients with hematological malignancies undergoing hematopoietic stem cell transplantation (HSCT), conditioning regimens containing high doses of alkylating drugs are used. This leads to premature gonadal failure in most women and men. The main predictors of ovarian function return include the patient's age at transplantation, AMH level, and the number of chemotherapy cycles [36].

Data on the impact of chemotherapy on fertility in patients with ovarian cancer are limited. In a small group of patients receiving mostly platinum derivatives in monotherapy, no ovarian dysfunction was observed [37]. On the other hand, in patients with non-epithelial ovarian cancer receiving BEP (etoposide, cisplatin, and bleomycin) or EP (etoposide, cisplatin) regimens, amenorrhea, and earlier menopause were more frequent [37].

Chemotherapy regimens used for colorectal cancer have an insignificant effect on fertility. There are no data on the risk of gonadotoxicity of taxanes or fluorouracil in men [25].

Table 2 presents the risk of gonadotoxicity disorders in women depending on the chemotherapy regimen.

Table 3 presents groups at risk of infertility after anticancer treatment in childhood.

Recommendations

1. Due to the gonadotoxicity of chemotherapy, it is recommended to use one of the methods of fertility protection before starting chemotherapy (III, A).
2. Fertility preservation methods with proven effectiveness include freezing of eggs, embryos, or ovarian tissue (II, A).
3. Non-hormonal or barrier contraception is recommended during chemotherapy (II, A).

Hormone therapy

Hormone therapy is routinely used in patients with early and advanced breast cancer, prostate cancer, and some gynecological cancers.

In patients with hormone-sensitive breast cancer postoperative hormone therapy is used for 5–10 years, depending on the cancer stage. In patients in the reproductive period, tamoxifen or aromatase inhibitors in combination with gonadoliberin analogs or tamoxifen alone are most often used. Tamoxifen often leads to menstrual disorders but does not affect AMH levels [38–40]. Data on the effect of this drug on the course of pregnancy and the health of children conceived during therapy are contradictory. Since tamoxifen may increase the risk of miscarriage and developmental defects (e.g., craniofacial malformations, genital defects), non-hormonal or barrier contraception is recommended during therapy and 3 months after its completion [41–43]. Gonadoliberin analogs cause temporary inhibition of ovarian function in approximately 85% of patients [44]. Menstruation returns in 90% of patients up to the age of 40 and much less often in older women [45].

So far, no gonadotoxic effects of tamoxifen and aromatase inhibitors in combination with a gonadoliberin analog have been reported. However, long-term hormone therapy postpones pregnancy; therefore, it is recommended to seek advice on securing fertility before starting treatment. There are two ways to increase the chances of getting pregnant: preserve eggs, embryos, or ovarian tissue before starting treatment, or temporarily stopping hormone therapy and trying to get pregnant in the meantime. The safety of this procedure was assessed in a study involving 518 patients with hormone-dependent breast cancer aged up to 42 years [46]. After 18–30 months of post-operative hormone therapy, it was interrupted for up to 2 years for patients to try to conceive, after which the treatment was continued for the originally planned duration. Preliminary results of the study indicate that a break in hormone therapy does not increase the risk of cancer recurrence; however, further observation is indicated.

Pregnancy after treatment of breast cancer, also expressing hormone receptors, does not worsen the prognosis or affect the health of the child [46].

Recommendations

1. Hormone therapy does not have a gonadotoxic effect, but due to its long duration, it delays conception. For this reason, patients should be advised to seek counseling and take measures to preserve fertility before starting treatment (II, C).
2. Fertility preservation methods with proven effectiveness include eggs, embryos, or ovarian tissue cryopreservation (II, A).
3. During adjuvant hormone therapy, non-hormonal or barrier contraception is recommended (II, A).
4. It is safe to become pregnant during a planned interruption of hormone therapy (II, C).

Molecularly targeted therapy

There are few data on gonadotoxicity induced by molecularly targeted drugs [25]. In patients with HER2-positive breast cancer, no effect of trastuzumab, lapatinib, and T-DM1 (trastuzumab emtansine) on gonadal function was found [47–49]. Less is known about the gonadotoxic effects of poly-(ADP-ribose) polymerase (PARP) inhibitors, cyclin-dependent kinase (CDK 4/6) inhibitors, and targeted drugs used in melanoma patients. In animal studies, testicular degeneration was observed in male rats receiving BRAF inhibitors — dabrafenib, encorafenib, cobimetinib, and a reduced number of oocytes in female rats receiving dabrafenib, trametinib, and cobimetinib [50].

There is some evidence that tyrosine kinase inhibitors (TKIs) may adversely affect oocyte and sperm maturation, gonadal function, and fertility. Treatment with imatinib impairs ovarian function; however, spontaneous pregnancies are observed during treatment with this drug; therefore, the use of effective contraception is recommended. Data on the effect of imatinib on male fertility are inconclusive. Over 90% of patients using this drug experienced a transient decrease in testosterone levels, and 20% developed gynecomastia [51].

In women receiving radioiodine (^{131}I) after surgical treatment for thyroid cancer with high risk of recurrence within a year, decreased AMH levels were observed [52, 53].

Recommendations

1. Most targeted therapies are not gonadotoxic, but data on this are sparse. Therefore, patients should be informed about the potential risk of fertility disorders and recommended methods of fertility preservation (IV, B).
2. During targeted therapy and several months after its completion, contraception is recommended (IV, A).

Immunotherapy

In the ovaries and testes, the physiological expression of programmed death receptor type 1 (PD-1) protein

Table 2. Gonadotoxicity risk of anti-cancer treatment in women (based on the European Society of Human Reproduction and Embryolog recommendations)

Degree of risk of amenorrhea after oncological treatment	Therapy
High risk (> 80%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P; TC] in breast cancer patients ≥ 40 years of age
	Conditioning regimens for HSCT with cyclophosphamide and/or TBI in patients with hematological malignancies
	Abdominal and pelvic radiotherapy with ovarian coverage
Intermediate risk (40–60%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P; TC] in breast cancer patients aged 30–39 years
	Regimens based on alkylating agents (e.g., MOPP, BEACOPP, CHOP, CHOPE) in patients with lymphoma
Low risk (< 20%)	Regimens containing cyclophosphamide [with anthracyclines and/or taxanes: (F)EC/(F)AC only or followed by T or P; TC] in breast cancer patients ≤ 30 years of age
	Non-alkylating regimens (e.g., ABVD or EBVP) in lymphoma patients ≥ 32 years of age
	BEP/EP in patients with non-epithelial ovarian cancer
	FOLFOX, XELOX, or capecitabine in colorectal cancer patients
	Multi-drug chemotherapy (EMA-CO and platinum-based regimens) for gestational trophoblastic disease
	Radioactive iodine (^{131}I) in thyroid cancer patients
Very low or no risk	*Vinca* alkaloids
	Targeted drugs (trastuzumab, lapatinib, and rituximab)
	Tamoxifen, GnRH analogs, aromatase inhibitors, medroxyprogesterone acetate, megestrol
	Non-alkylating chemotherapy regimens (e.g., ABVD or EBVP) in lymphoma patients < 32 years of age
	Methotrexate monotherapy
Unknown risk	Chemotherapy containing platinum derivatives and taxoids in patients with gynecological and lung cancer
	Most targeted therapies (monoclonal antibodies, PARP inhibitors, CDK4/6 inhibitors, tyrosine kinase inhibitors) and immunotherapy

(F)EC/(F)AC — 5-fluorouracil, epirubicin/doxorubicin, cyclophosphamide; ABVD — doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP — cyclophosphamide, doxorubicin, vincristine, bleomycin, etoposide, procarbazine, prednisone; BEP — etoposide, cisplatin, bleomycin; CHOP — cyclophosphamide, doxorubicin, vincristine, prednisone; CHOPE — CHOP, etoposide; EBVP — epirubicin, bleomycin, vinblastine, prednisone; EMA-CO — etoposide, actinomycin D, methotrexate, followed by cyclophosphamide and vincristine; EP — etoposide, cisplatin; FOLFOX — 5-fluorouracil, oxaliplatin; GnRH analog — analog of gonadotropin-relea sing hormone; HSC — hematopoietic stem cells; MOPP — mechlorethamine, vincristine, procarbazine, prednisone; P — paclitaxel; PARP — poly-(ADP-ribose) polymerase T — docetaxel; TBI — total body irradiation; XELOX — capecitabine, oxaliplatin

and its ligand (PD-L1, programmed death ligand 1) is low. The use of immune checkpoint inhibitors (ICIs) may lead to various hormonal disorders, including primary and secondary hypogonadism, secondary sexual disorders, and decreased libido [54]. So far, the direct impact of ICIs on the ovarian reserve and reproductive potential of men has not been determined, but a few reports indicate autoimmune testicular damage leading to azoospermia [55].

PD-L1 is strongly expressed in the placenta, but no direct teratogenic effect of ICIs on the fetus has been demonstrated. The activated immune response may lead to miscarriage, inhibit fetal growth, or cause immune-mediated adverse reactions in the fetus or mother. For this reason, the use of ICIs in pregnant women is not recommended [55]. In pregnant patients with metastatic cancer (e.g., melanoma), decisions should be made individually, taking into account the dynamics of the disease and available treatment options.

Stimulation of a woman's immune system, even for many months after therapy completion, may reduce the immune tolerance of the developing fetus or cause reproductive failure in the future. For this reason, contraception is recommended during therapy and for 5 months after its completion [56].

Recommendations

1. Fertility counseling is recommended before starting immunotherapy (IV, C).
2. Immunotherapy is not recommended in pregnant women (IV, C).

Table 3. The risk of infertility depending on the type of cancer and treatment in children

Low risk (< 20%)	Intermediate risk	High risk (> 80%)
Acute lymphoblastic leukemia	Acute myeloid leukemia	Total body irradiation
Stage I soft tissue sarcomas	hepatoblastoma	Pelvic or testicular radiotherapy
Germinal tumors (without radiotherapy and with gonad preservation)	Ewing's sarcoma without metastasis	Conditioning chemotherapy prior to bone marrow/stem cell transplantation
Retinoblastoma	Osteosarcoma	Hodgkin's lymphoma (with use of alkylating agents)
Brain tumors (surgery +/– radiotherapy < 24 Gy)	Brain tumors, spinal radiotherapy, brain > 24 Gy	Stage IV soft tissue sarcomas
	Stage II–III soft tissue sarcomas	Ewing's sarcoma with metastases
	Non-Hodgkin's lymphomas	
	Hodgkin lymphoma	

3. Contraception is recommended during immunotherapy and for 5 months after its completion (IV, C).

Fertility protection in women

Along with the growing incidence of cancer, also among women of reproductive age, and the delayed delivery of the first child, the number of women diagnosed with cancer who plan to start or enlarge a family is growing. Fertility preservation should be an integral part of oncological care.

When choosing a method of fertility protection, the patient's reproductive potential and expectations, clinical situation, and having a partner should be taken into account. The decision should be made by the patient, possibly in consultation with his/her partner, after obtaining full information on this subject from a team consisting of an oncologist, a reproductive medicine doctor, a psychologist, and, if necessary, a geneticist. The decision-making algorithm regarding the choice of the method or methods of fertility preservation is presented in Figure 1.

Pharmacological ovarian suppression

Ovarian suppression using GnRH analogs can be used in any case of risk of fertility loss due to chemotherapy. Although the protective mechanism of action of these drugs has not been fully elucidated, their efficacy and safety have been confirmed in several randomized clinical trials [57, 58].

Most of the studies involved patients with breast cancer. A meta-analysis published in 2018 showed that the use of GnRH analogs during chemotherapy increased the chance of getting pregnant almost two-fold [59]. The percentage of pregnancies in the range of 5–10% indicates, however, that this method is rather complementary in patients with breast cancer but is insufficient to preserve fertility. The protective effect of GnRH has not been found in patients with lymphomas [60]. On the other hand, in patients with ovarian cancer, GnRH analogs used together with chemotherapy reduced the risk of ovarian failure [61].

Ovarian transposition before radiotherapy

The evidence for the effectiveness of ovarian transposition is based on small retrospective studies. Ovarian transposition before planned radiotherapy should be performed in a minimally invasive manner. In selected situations, an alternative may be to shield the ovaries during irradiation.

Ovarian tissue cryopreservation

Ovarian tissue freezing (cryopreservation) is still an experimental procedure in Poland. The advantage of autotransplantation of ovarian tissue is the restoration of its natural functions and proper hormonal balance and the possibility for patients to get pregnant naturally. In addition, this method can be used in patients who have already started chemotherapy. However, in such a situation, stimulation and collection of mature oocytes is not recommended due to the risk of damaging their genetic material during chemotherapy. Since the activity of the ovarian tissue has to be maintained for a long time, it is not recommended to freeze it by vitrification, but rather slowly [62].

Oocyte (or embryos) cryopreservation — stimulation of ovulation and eggs retrieval

The most commonly used and most effective method of fertility protection is stimulation of ovulation and the collection of oocytes and their freezing or *in vitro* fertilization and freezing of embryos. In the case

of hormone-dependent tumors, stimulation with an aromatase inhibitor or progesterone may be used. The effectiveness of this method depends to a large extent on the patient's age and her ovarian reserve (number and quality of available oocytes), assessed based on the serum AMH level and the number of antral follicles in the sonographically visualized ovaries.

Oocyte *in vitro* maturation (IVM)

When preparing ovarian tissue for freezing, immature oocytes can be harvested and then prepared for *in vitro* maturation (IVM); however, this method is still experimental.

Recommendations

1. Before gonadotoxic oncological treatment, it is recommended to assess the AMH level (preferably after discontinuation of any drugs affecting the concentration of sex hormones or contraceptives) (III, A).
2. In patients with breast cancer, regardless of its subtype, GnRH analogs are recommended during chemotherapy. These drugs should not be used routinely in patients with cancers other than breast cancer (I, A).
3. In women with sufficient ovarian reserve and no risk of ovarian metastases, ovarian transposition may be used before pelvic radiotherapy, and gonadal shielding may be used in selected patients (IV, C).
4. In women at risk of gonadotoxic effects, ovarian tissue freezing (II, A) may be additionally considered. Relative contraindications include limited ovarian reserve, age > 36 years (III, B), and hematological, pelvic, and other cancers with high risk of gonadal metastasis (III, A). Freezing of ovarian tissue is the most effective method of protecting fertility in women who have already started chemotherapy or who had started chemotherapy up to 6 months earlier (IV, A).
5. If the start of oncological treatment can be postponed by about 2 weeks, the basic method of fertility protection is the collecting and freezing of oocytes (II, A).
6. A patient with a partner may be offered embryo freezing with possible simultaneous oocyte and embryo freezing (IV, A).
7. If rapid initiation of oncological treatment is necessary, stimulation should be started regardless of the phase of the menstrual cycle. Multiple stimulations result in more eggs in less time (III, A). In hormone-dependent tumors, stimulation with an aromatase inhibitor or progesterone may be used (III, A).

Fertility protection in men

The consequence of cancer, radiotherapy, systemic treatment, or surgical treatment may cause temporary or permanent male infertility [63–64]. The resumption of spermatogenesis depends on the type of treatment, its intensity, and individual sensitivity. It is important that before starting treatment, preferably after diagnosis, the medical team, with the participation of a reproductive medicine specialist, presents the patient with options for preserving fertility [65].

The most effective method of reducing the risk of infertility in men is freezing semen obtained by masturbation. It is important to secure more than one sample [66]. Before freezing, a semen sample should be collected for testing to exclude carriers of infectious diseases and to assess its quality. In many patients, the semen quality deviates from the normal values before starting oncological treatment [67]. A chance for fertilization, even with a small number of male reproductive cells, is given by intracytoplasmic sperm injection (ICSI) [66–68].

Sperm collection may be supported by phosphodiesterase type 5 inhibitors used in the treatment of erectile dysfunction [69]. If neurological disorders or psychogenic anejaculation are the cause that makes sperm donation difficult, penile vibratory stimulation (PVS) can be used, while in the case of damage to the ejaculatory reflex arc, electrostimulation may be indispensable (both procedures are rarely performed in Poland) [70, 71]. In men with retrograde ejaculation, semen collection attempts begin with oral administration of sympathomimetic drugs, anticholinergics, or a combination thereof. If these methods are ineffective, sperm can be obtained after masturbation and prior alkalization of the urine [72].

If sperm cannot be obtained by masturbation (e.g. as a result of azoospermia or cryptozoospermia), a fragment of the testicle can be surgically removed [73]. Once selected, the sperm are frozen and used for *in vitro* fertilization (IVF/ICSI).

Gonadoliberin analogs have not been demonstrated to protect fertility in males; therefore, the use of this method is unjustified [74].

A special group includes patients with hematological or testicular cancers, in whom autologous transplantation of frozen testicular cells or tissues carries the risk of cancer dissemination. Research is currently underway on the transplantation of allogeneic testicular cells or tissues and the *ex vivo* culture of mature spermatozoa derived from stem cells [68].

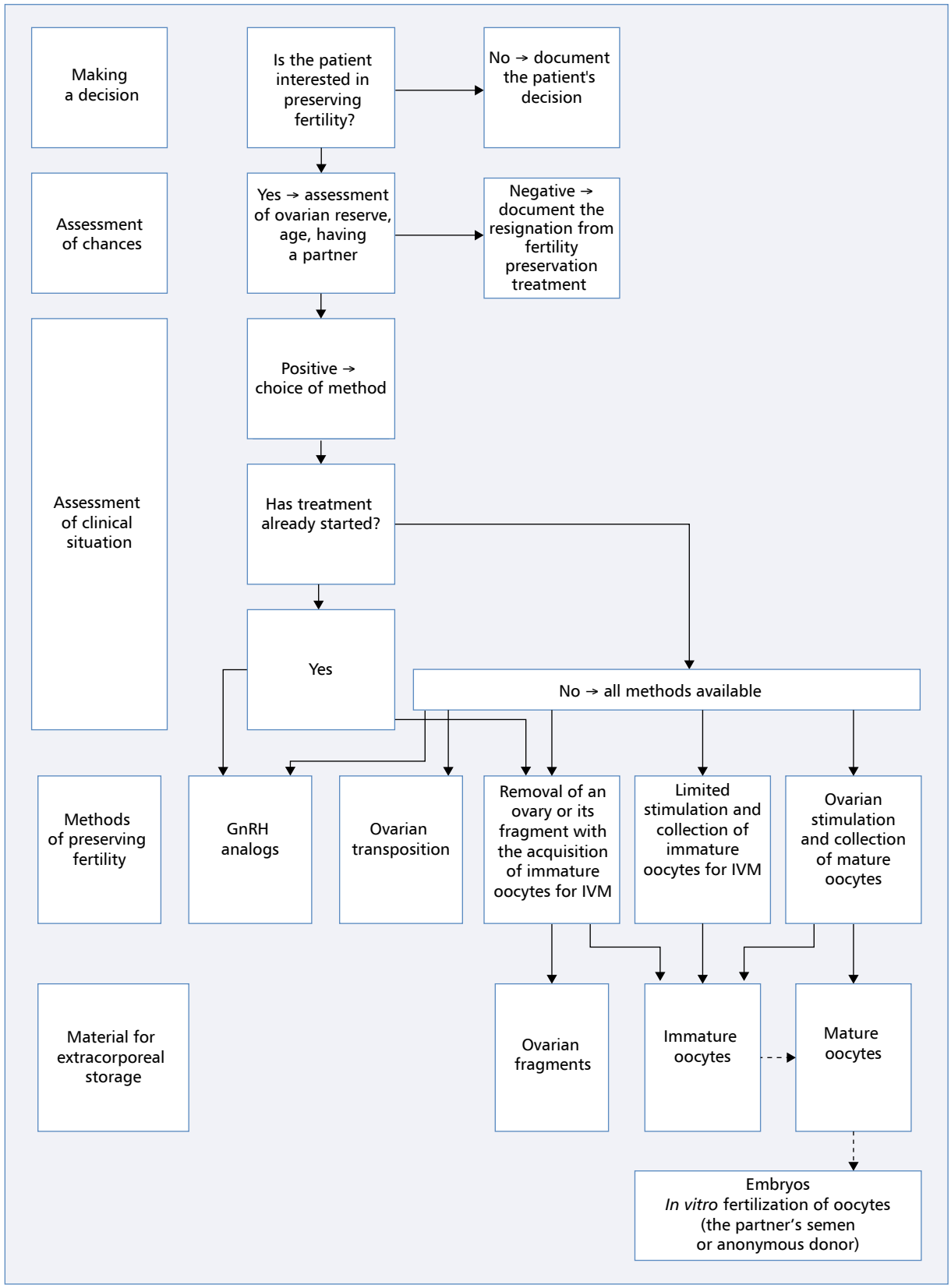

Figure 1. Algorithm for management of fertility preservation in women; GnRH — gonadotropin-releasing hormone; IVM — *in vitro* maturation

Recommendations

1. Semen freezing should be offered to every man of childbearing age before starting oncological treatment. The most effective form is obtaining sperm from the ejaculate (II, A).
2. In exceptional cases, an attempt can be made to surgically obtain sperm from the testicles (IV, C).
3. The use of hormonal protection of spermatogenesis is not recommended (III, B).

Fertility protection in children

In developed countries, over 80% of children with cancer are cured or achieve long-term remission. However, 60–85% of convalescents experience adverse effects of chemo- and/or radiotherapy, including damage to the gonads or infertility. Fertility disorders may result from radio- and/or chemotherapy and surgical treatment [75].

Ovarian and testicular tissue freezing is used to preserve fertility in children receiving chemotherapy, and sperm and egg cells are frozen when they reach maturity. In children receiving radiotherapy, gonadal shields, and ovarian transposition are used.

Testicular tissue freezing is an experimental method and is only used when a semen sample cannot be obtained. The whole or part of the removed testicle may be frozen. An open biopsy of the testis is usually preferred.

In prepubertal girls, the ovaries cannot be stimulated to produce mature eggs. On the other hand, there is no unequivocal evidence confirming the possibilities for pregnancy and delivery as a result of cryopreservation of ovarian tissue collected in the prepubertal period. Such information should be provided to patients and their legal guardians. This is especially true for tumors that may metastasize to the ovaries or, as in the case of leukemia, frozen tissue can contain tumor cells [76].

Once they are mature enough to produce eggs or sperm, the treatment of children is the same as that of adults, except that embryo production is excluded.

The age of spermarche in boys ranges from 10 to 16 years old — usually around 12 years old. Semen for freezing is obtained by masturbation, after obtaining consent of the legal guardian. If obtaining a semen sample in sexually mature boys is not possible, sperm extraction from the testicle and their future use for *in vitro* fertilization using micromanipulation may be considered.

Recommendations

1. It is necessary to inform parents, guardians, and patients — depending on their age — about the possibility of fertility disorders resulting from anticancer treatment, as well as about the possibility of fertility preservation (IV, A).
2. Multidisciplinary cooperation is required, i.e., the establishment of an oncofertility team with the participation of a pediatric oncohematologist, pediatric endocrinologist, reproductive medicine physician, urologist, psychologist, and a specialized nurse. The management plan for patients at prepubertal age is shown in Figure 2 (IV, A).
3. Oocyte or sperm freezing should be offered to any patient at risk of infertility who is eligible for these methods (II, A).
4. Prepubertal children and their legal guardians should be informed that available methods of fertility protection are experimental and may have limited effectiveness (IV, A).
5. In sexually mature individuals in whom sperm cannot be obtained from the ejaculate, freezing of testicular tissue should be considered (IV, C).

Preimplantation genetic diagnostics

Preimplantation diagnostics include genetic testing of embryos before they are transferred to the uterine cavity. Depending on the purpose, it can be used to detect single gene disorders (e.g., point mutations), structural chromosome abnormalities (e.g., translocations), quantitative chromosome disorders (aneuploidies), and predisposition to genetic diseases of polygenic etiology. Patients should be informed that a "normal" or negative preimplantation genetic test result does not guarantee the absence of genetic disorders in the newborn. Performing a preimplantation test does not exclude the need to perform prenatal tests when indicated.

Biopsy of polar bodies (small fragments of cells separated from the oocyte during meiotic division) or embryos (both on the 3rd and 5th–6th day of development), and even performing them sequentially on a single embryo, does not pose a threat to the embryo and the child born from it [77].

Preimplantation testing for monogenic diseases occurring in adults is ethically justified if diseases are serious, the methods of their prevention and treatment are unknown, or when the available methods are ineffective or perceived as very burdensome [78].

It is recommended that before starting preimplantation diagnostics, each patient should have the opportunity to consult a clinical geneticist and, if necessary, an oncologist and a psychologist, and that they should jointly decide on the scope of the planned diagnosis.

Being a carrier of a mutation that increases cancer risk does not exclude the presence of other genetic diseases, such as some rare diseases. As part of the screening, it is recommended to perform a basic test for mutations occurring in all ethnic groups, including in the *CFTR*, *SMA,* and *FMR1* genes, and to extend

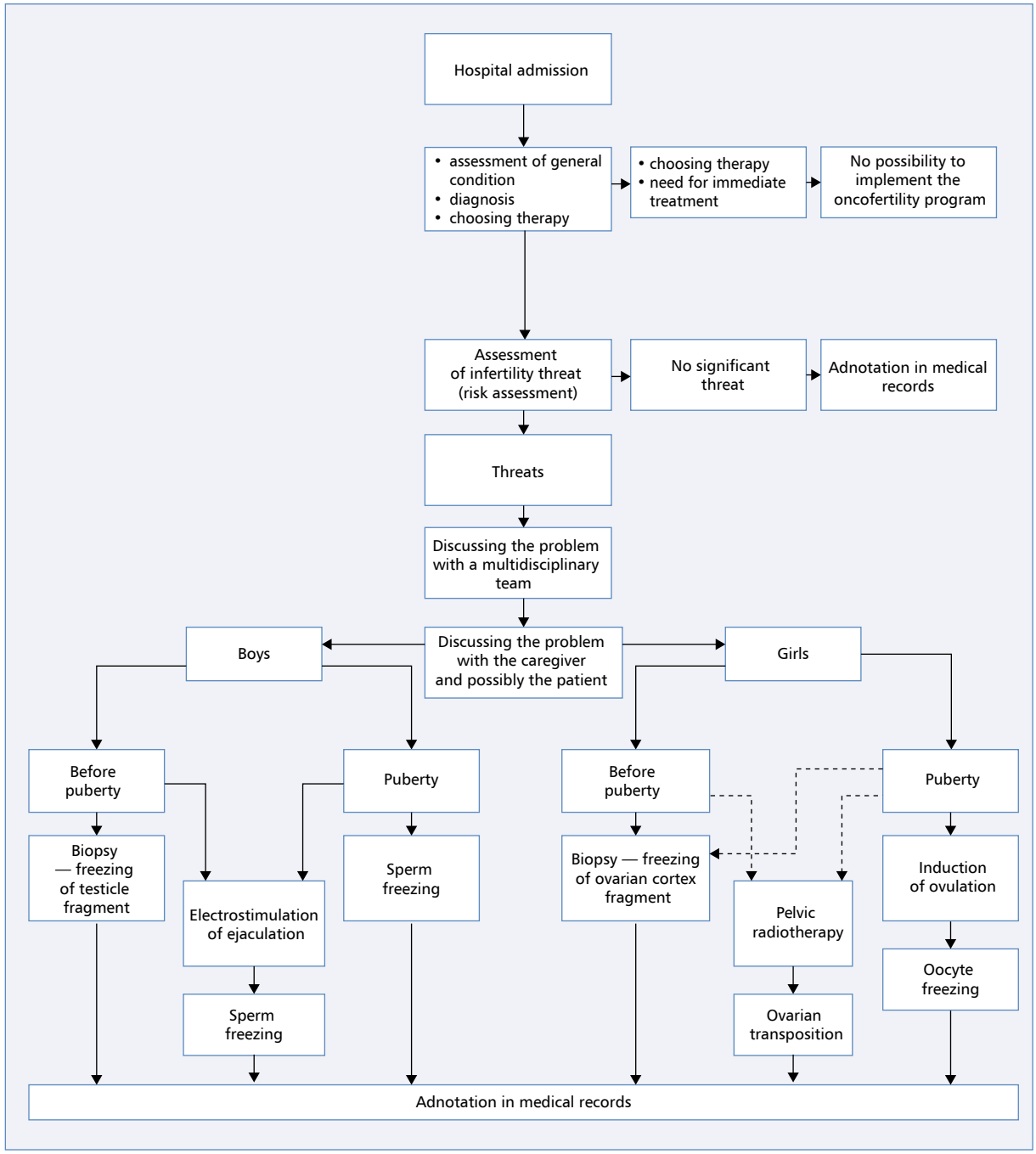

Figure 2. Algorithm for fertility management protection in prepubertal patients

the diagnostics depending on ethnic origin. The second group of disorders that require additional tests as part of preimplantation diagnostics are aneuploidies, i.e., an abnormal number of chromosomes in a cell. The risk of these disorders increases with the mother's age, so it is of particular importance in women with a history of cancer, which usually postpones motherhood for several years.

Preimplantation diagnostics, by removing the genetic etiology of cancer diseases, breaks the chain of their familial occurrence, minimizes the risk of rare diseases, and prevents genetic diseases related to the mother's age (e.g., Down syndrome, Edwards syndrome, or Patau syndrome).

It should be remembered that as a result of the diagnostics, only a part of the examined embryos will meet the criteria for transfer. Embryos with genetic abnormalities

are not transferred and remain frozen. It should also be remembered that only some of the healthy embryos are implanted in the uterus, which limits the effectiveness of attempts to conceive [79].

Recommendations

1. Carriers of pathogenic gene variants with high risk of cancer should receive detailed information on preimplantation genetic testing (IV, C).
2. Each woman who decides to undergo preimplantation diagnostics has to consult a clinical geneticist, and if necessary, an oncologist and a psychologist to jointly decide on the scope of diagnostics (IV, C).
3. Patients should be advised that a "normal" preimplantation genetic test result does not guarantee the absence of genetic abnormalities in the child (IV, C).

Legal aspects of fertility protection in cancer patients

The possibility of impaired fertility related to oncological treatment imposes certain information obligations on the doctor. The Act on Infertility Treatment defines, among others, the principles of protection of the embryo and reproductive cells in this clinical situation, as well as methods of infertility treatment, including medically assisted procreation [80]. The Act allows *in vitro* fertilization of no more than six female reproductive cells. If the recipient reaches the age of 35 or has a disease coexisting with infertility or has failed *in vitro* fertilization twice, it is possible to fertilize more female reproductive cells, but this information should be recorded in the medical documentation. The Act prohibits the use of male and female reproductive cells from a deceased donor in assisted procreation [81].

The patient's consent is a prerequisite for providing a health service, including the procedure of assisted procreation. A minor patient who is over 16 years of age has the right not to consent to an examination or other health services despite the consent of his legal representative or actual guardian. In this case, the law specifies that guardianship court authorization is required.

The Act on the Professions of Physician and Dentist imposes an obligation on the physician to provide the patient or his/her statutory representative with accessible information about the patient's health condition, diagnosis, proposed and possible diagnostic and treatment methods, foreseeable consequences of their use or omission, treatment results, and prognosis. The Act also requires the doctor to provide the patient with full information about the risks associated with fertility, including in particular difficulties in getting pregnant. This information should be documented in medical records. Violation of this obligation may result in the unlawfulness of therapies implemented with regard to the patient and result in the physician's liability [82].

Eggs cryopreservation is legally permissible. The Act on Infertility Treatment formulates the donor's right to dispose of oocytes, including the right to demand their destruction.

Embryos capable of proper development resulting from reproductive cells collected for partner or non-partner donation, which have not been used in the assisted procreation procedure, must be stored in conditions ensuring their proper protection until transferred to the recipient's body.

If both donors die, the embryos are transferred to an anonymous donation program. It is inadmissible to destroy embryos capable of normal development and not transferred to the recipient's body, and it does not have to be the person in whom the implantation of the embryo was originally supposed to take place [83].

Recommendations

1. The patient has the right to consent to the provision of health services, including assisted procreation techniques (IV, A).
2. No more than six female reproductive cells may be fertilized. If the recipient reaches the age of 35, is diagnosed with a disease coexisting with infertility, or has had two ineffective *in vitro* fertilization treatments, it is possible to fertilize more female reproductive cells, in which case the reason should be documented in the patient's medical records (IV, A).
3. The semen of the deceased must not be used in the procedure of insemination and the procedure of medically assisted procreation (IV, A).
4. Embryos incapable of normal development must not be used (IV, A).

Psychological aspects of fertility protection in cancer patients

The risk of losing fertility associated with oncological treatment and making decisions about its protection cause stress and anxiety, and, in the case of abandoning the attempt to preserve fertility, long-term regret. The adverse effects of this situation can be reduced by supporting teams involving doctors, psychologists, and other healthcare professionals. Communication with the patient should be adapted to his/her age and life situation and should also include his/her family [84]. The information provided should cover medical procedures, risks, benefits, chances of success, and costs. The participation of the patient's partner and family may be useful in discussing all aspects related to fertility [85, 86].

Recommendations

1. A clinical psychologist should be part of the multidisciplinary team dealing with fertility preservation in cancer patients (IV, C).
2. Depending on the patient's situation, the cancer patient's partner and other family members should be involved in the decision-making process about fertility preservation (IV, C).

Pregnancy after cancer

The increasing age of mothers giving birth to children is accompanied by a growing desire to have children after being cured of cancer [25]. Most data on pregnancy after cancer treatment concerns patients with breast cancer. They indicate that pregnancy is possible and safe in this group. This also applies to women diagnosed with hormone-dependent breast cancer. Cured patients should be informed that pregnancy, time from cancer diagnosis to pregnancy, or breastfeeding do not affect the risk of recurrence and that in breast cancer it is safe to interrupt postoperative hormonal therapy to become pregnant.

However, there is an increased risk of obstetric and childbirth complications in women after oncological treatment, including prematurity, low birth weight, delivery by cesarean section (elective or emergency), assisted delivery, or postpartum hemorrhage. The risk of complications seems to be higher if the interval between oncological treatment completion and pregnancy is short [87]. For this reason, close monitoring of pregnancies after cancer treatment is recommended. In addition, at least a one-year break from chemotherapy cessation is recommended before trying to get pregnant. In patients using other anticancer drugs, a break should be considered, taking into account the type of therapy (e.g. 3 months in the case of tamoxifen, 5 months in the case of immunotherapy, and BRAF/MEK inhibitors, 7 months in the case of trastuzumab) [47, 50, 88].

Assisted reproductive technology after cancer treatment may be considered with caution if there is difficulty in conceiving. An increase in oncological risk in patients after breast cancer treatment cannot be ruled out by current data [89, 90].

There were no differences in the course of pregnancy in female partners of men after oncological treatment.

Recommendations

1. Consultation on the safety of pregnancy after oncological treatment should take into account the type of cancer, previous treatment, and the patient's situation (IV, A).
2. Patients who have undergone successful cancer treatment should not be discouraged from becoming pregnant (IV, A).
3. An adequate interval between the end of cancer therapy and attempts to get pregnant is recommended (III, B).
4. In patients with breast cancer, especially those with low risk of recurrence, interruption of postoperative hormone therapy may be considered to get pregnant (II, C).
5. Pregnancies of women after cancer treatment should be carefully monitored due to the potential increased risk of obstetric and childbirth complications (IV, B).
6. There are no contraindications to breastfeeding in patients who have completed oncological treatment (IV, B).

Health of children of mothers who received oncological treatment during pregnancy

Cancer affects about 1 in 1000 pregnant women. Treatment of pregnant women should not differ significantly from standard therapy but should be adapted to the gestational age and state of the mother's health. The teratogenic effect of some drugs (e.g., chemotherapy, targeted drugs, or hormone therapy) should be taken into account. Termination of pregnancy does not improve the prognosis of affected women [91].

The effects of chemotherapy depend on the gestational age at the start of treatment. Therapy initiated within the first 10 days after fertilization is associated with high risk of damage to totipotent or pluripotent cells, which may lead to miscarriage [92]. The use of chemotherapy in the first trimester of pregnancy, especially during organogenesis (5–8 weeks), is also associated with increased risk of congenital malformations (7.5–17% compared with a population risk of 4.1–6.9%). The risk of birth defects associated with the initiation of chemotherapy in the second and third trimesters is 3–7.5%, which corresponds to the population risk [93].

In children born within 2 weeks of chemotherapy completion, abnormalities in peripheral blood counts may occur due to transient myelosuppression (leukopenia, anemia, and thrombocytopenia). Therefore, it is recommended to administer the last course of chemotherapy at least 3 weeks before the planned delivery [92]. The offspring of mothers treated with rituximab may have a selective transient B-cells deficiency. No increased susceptibility to infection was observed, and response to vaccination was normal. Oligohydramnios and pulmonary hypoplasia have been observed in children of mothers treated with trastuzumab during

pregnancy; therefore, the use of this drug during pregnancy is not recommended. Data on the use of tamoxifen in pregnancy are conflicting, cases of miscarriage or abnormal pregnancy have been reported; therefore, its use in pregnant women is not recommended.

Chemotherapy administered during pregnancy increases the risk of premature birth and low birth weight in newborns; however, these deficiencies are usually compensated for in further development. However, chemotherapy can adversely affect the child's physical and neurological development. In some studies, attention was paid to the occurrence of problems with concentration, emotional disorders, especially attacks of aggression, and somatic complaints at school age [94]. However, no cardiac complications have been observed in children of mothers who received anthracyclines during pregnancy, although this risk cannot be completely excluded. Hearing loss has been reported in children of mothers who received cisplatin during pregnancy [94]. An increased risk of secondary cancers has not been observed in children of mothers who received chemotherapy during pregnancy, but data on this are scarce [94].

Recommendations

1. Due to the risk of congenital defects in children, chemotherapy should not be used in the first trimester of pregnancy (III, A).
2. Prematurity may be associated with impaired neuropsychological development; therefore, apart from absolute obstetric and gynecological indications or the mother's health status, in women receiving oncological treatment, induction of premature labor is not recommended (I, A).
3. In order to reduce the risk of transient hematological complications in neonates, the last course of chemotherapy should be scheduled at least 3 weeks before the expected delivery date (III, A).
4. Children of mothers receiving oncological treatment during pregnancy should be provided with multidisciplinary care (neonatological and pediatric, cardiological, neurological, ophthalmological, laryngological, and psychological) (IV, A).

Article Information and Declarations

Financing

None.

Acknowledgments

None.

Conflict of interest

J.K.-G.: received fees for consultations/lectures/training and fees for participation in scientific congresses from Roche, Novartis, Pfizer, Gelead, Eli Lilly, Celonpharma, Organon, Astra Zeneca, Teva, Accord.
K.Ł.: received fees for consultations/lectures/training and fees for participation in scientific congresses from Organon, Ferring.
P.J.: received fees for consultations/lectures/training and fees for participation in scientific congresses from Organon, IBSA, Gedeon, Ferring.
K.P.: received fees for consultations/lectures/training/clinical research and fees for participation in scientific congresses from AstraZeneca, Gilead, Eli Lilly, Pfizer, MSD, Teva, Egis, Roche, Vipharm, Novartis.
S.W.: received fees for consultations/lectures/training and fees for participation in scientific congresses from Merck, IBSA.
J.J.: participation in advisory committees of AstraZeneca, Exact Sciences, MSD; lectures for AstraZeneca, MSD, Gilead, Pfizer (without fee); conference participation fees from Takeda.
The other authors have not reported a conflict of interest.

References

1. Wojciechowska W, Barańska K, Michałek I, et al. Nowotwory złośliwe w Polsce w 2020 roku. Ministerstwo Zdrowia, Warszawa. https://onkologia.org.pl/sites/default/files/publications/2023-01/nowotwory_2020.pdf (30.03.2023).
2. Knudson AG. Overview: genes that predispose to cancer. Mutat Res. 1991; 247(2): 185–190, doi: 10.1016/0027-5107(91)90013-e, indexed in Pubmed: 2011135.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674, doi: 10.1016/j.cell.2011.02.013, indexed in Pubmed: 21376230.
4. Bashyam MD, Animireddy S, Bala P, et al. The Yin and Yang of cancer genes. Gene. 2019; 704: 121–133, doi: 10.1016/j.gene.2019.04.025, indexed in Pubmed: 30980945.
5. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009; 458(7239): 719–724, doi: 10.1038/nature07943, indexed in Pubmed: 19360079.
6. McClellan J, King MC. Genetic heterogeneity in human disease. Cell. 2010; 141(2): 210–217, doi: 10.1016/j.cell.2010.03.032, indexed in Pubmed: 20403315.
7. Filippi F, Peccatori F, Manoukian S, et al. Fertility Counseling in Survivors of Cancer in Childhood and Adolescence: Time for a Reappraisal? Cancers (Basel). 2021; 13(22), doi: 10.3390/cancers13225626, indexed in Pubmed: 34830781.
8. Jones G, Hughes J, Mahmoodi N, et al. What factors hinder the decision-making process for women with cancer and contemplating fertility preservation treatment? Hum Reprod Update. 2017; 23(4): 433–457, doi: 10.1093/humupd/dmx009, indexed in Pubmed: 28510760.
9. Kufel-Grabowska J, Podolak A, Maliszewski D, et al. Fertility Counseling in -Mutated Women with Breast Cancer and Healthy Individuals. J Clin Med. 2022; 11(14), doi: 10.3390/jcm11143996, indexed in Pubmed: 35887761.
10. Jach R, Pabian W, Spaczyński R, et al. Recommendations of the Fertility Preservation Working Group in Oncological, Hematological and Other Patients Treated With Gonadotoxic Therapies "ONCOFERTILITY" (GROF) of the Polish Society of Oncological Gynecology. J Adolesc Young Adult Oncol. 2017; 6(3): 388–395, doi: 10.1089/jayao.2017.0039, indexed in Pubmed: 28657411.
11. Ethics Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org. Fertility preservation and reproduction in patients facing gonadotoxic therapies: an Ethics Committee opinion. Fertil Steril. 2018; 110(3): 380–386, doi: 10.1016/j.fertnstert.2018.05.034, indexed in Pubmed: 30098684.
12. Anderson RA, Amant F, Braat D, et al. ESHRE Guideline Group on Female Fertility Preservation. ESHRE guideline: female fertility prese-

rvation. Hum Reprod Open. 2020; 2020(4): hoaa052, doi: 10.1093/hropen/hoaa052, indexed in Pubmed: 33225079.
13. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019; 30(5): 672–705, doi: 10.1093/annonc/mdz062, indexed in Pubmed: 31046081.
14. Basta A, Bidziński M, Bieńkiewicz A, et al. Recommendation of the Polish Society of Oncological Gynecology on the diagnosis and treatment of epithelial ovarian cancer. Oncol Clin Pract. 2015; 11: 233–243.
15. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016; 27(1): 16–41, doi: 10.1093/annonc/mdv484, indexed in Pubmed: 26634381.
16. Kyrgiou M, Arbyn M, Bergeron C, et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). Br J Cancer. 2020; 123(4): 510–517, doi: 10.1038/s41416-020-0920-9, indexed in Pubmed: 32507855.
17. Trost L, Brannigan R. Fertility Preservation in Males. In: Gracia C, Woodruff T. ed. Oncofertility Medical Practice. Springer, New York, NY 2012.
18. Ståhl O, Eberhard J, Jepson K, et al. Sperm DNA integrity in testicular cancer patients. Hum Reprod. 2006; 21(12): 3199–3205, doi: 10.1093/humrep/del292, indexed in Pubmed: 16931803.
19. Ash P. The influence of radiation on fertility in man. Br J Radiol. 1980; 53(628): 271–278, doi: 10.1259/0007-1285-53-628-271, indexed in Pubmed: 6991051.
20. Marci R, Mallozzi M, Di Benedetto L, et al. Radiations and female fertility. Reprod Biol Endocrinol. 2018; 16(1): 112, doi: 10.1186/s12958-018-0432-0, indexed in Pubmed: 30553277.
21. Silvestris E, Cormio G, Skrypets T, et al. Novel aspects on gonadotoxicity and fertility preservation in lymphoproliferative neoplasms. Crit Rev Oncol Hematol. 2020; 151: 102981, doi: 10.1016/j.critrevonc.2020.102981, indexed in Pubmed: 32485429.
22. Mahajan N. Fertility preservation in female cancer patients: An overview. J Hum Reprod Sci. 2015; 8(1): 3–13, doi: 10.4103/0974-1208.153119, indexed in Pubmed: 25838742.
23. Littley MD, Shalet SM, Beardwell CG, et al. Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf). 1989; 31(3): 363–373, doi: 10.1111/j.1365-2265.1989.tb01260.x, indexed in Pubmed: 2559824.
24. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol. 2002; 187(4): 1070–1080, doi: 10.1067/mob.2002.126643, indexed in Pubmed: 12389007.
25. Lambertini M, Peccatori FA, Demeestere I, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2020; 31(12): 1664–1678, doi: 10.1016/j.annonc.2020.09.006, indexed in Pubmed: 32976936.
26. Perachino M, Massarotti C, Razeti MG, et al. Gender-specific aspects related to type of fertility preservation strategies and access to fertility care. ESMO Open. 2020; 5(Suppl 4): e000771, doi: 10.1136/esmoopen-2020-000771, indexed in Pubmed: 33115753.
27. Clemons M, Simmons C. Identifying menopause in breast cancer patients: considerations and implications. Breast Cancer Res Treat. 2007; 104(2): 115–120, doi: 10.1007/s10549-006-9401-y, indexed in Pubmed: 17061039.
28. NCCN Clinical Practice Guidelines in Oncology. Adolescent and Young Adult (AYA) Oncology, version 1.2023. https://www.nccn.org/(30.03.2023).
29. Lambertini M, Campbell C, Bines J, et al. Adjuvant Anti-HER2 Therapy, Treatment-Related Amenorrhea, and Survival in Premenopausal HER2--Positive Early Breast Cancer Patients. J Natl Cancer Inst. 2019; 111(1): 86–94, doi: 10.1093/jnci/djy094, indexed in Pubmed: 29878225.
30. Ejlertsen B, Tuxen MK, Jakobsen EH, et al. Adjuvant Cyclophosphamide and Docetaxel With or Without Epirubicin for Early TOP2A--Normal Breast Cancer: DBCG 07-READ, an Open-Label, Phase III, Randomized Trial. J Clin Oncol. 2017; 35(23): 2639–2646, doi: 10.1200/JCO.2017.72.3494, indexed in Pubmed: 28661759.
31. Lambertini M, Ceppi M, Cognetti F, et al. MIG and GIM study groups. Dose-dense adjuvant chemotherapy in premenopausal breast cancer patients: A pooled analysis of the MIG1 and GIM2 phase III studies. Eur J Cancer. 2017; 71: 34–42, doi: 10.1016/j.ejca.2016.10.030, indexed in Pubmed: 27951450.
32. van der Kaaij MAE, Heutte N, Meijnders P, et al. Premature ovarian failure and fertility in long-term survivors of Hodgkin's lymphoma: a European Organisation for Research and Treatment of Cancer Lymphoma Group and Groupe d'Etude des Lymphomes de l'Adulte Cohort Study. J Clin Oncol. 2012; 30(3): 291–299, doi: 10.1200/JCO.2011.37.1989, indexed in Pubmed: 22184372.
33. Meissner J, Tichy D, Katzke V, et al. Long-term ovarian function in women treated with CHOP or CHOP plus etoposide for aggressive lymphoma. Ann Oncol. 2015; 26(8): 1771–1776, doi: 10.1093/annonc/mdv227, indexed in Pubmed: 25962442.
34. Sieniawski M, Reineke T, Josting A, et al. Assessment of male fertility in patients with Hodgkin's lymphoma treated in the German Hodgkin Study Group (GHSG) clinical trials. Ann Oncol. 2008; 19(10): 1795–1801, doi: 10.1093/annonc/mdn376, indexed in Pubmed: 18544558.
35. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst Monogr. 2005(34): 12–17, doi: 10.1093/jncimonographs/lgi003, indexed in Pubmed: 15784814.
36. Akhtar S, Youssef I, Soudy H, et al. Prevalence of menstrual cycles and outcome of 50 pregnancies after high-dose chemotherapy and auto-SCT in non-Hodgkin and Hodgkin lymphoma patients younger than 40 years. Bone Marrow Transplant. 2015; 50(12): 1551–1556, doi: 10.1038/bmt.2015.178, indexed in Pubmed: 26237168.
37. Ceppi L, Galli F, Lamanna M, et al. Ovarian function, fertility, and menopause occurrence after fertility-sparing surgery and chemotherapy for ovarian neoplasms. Gynecol Oncol. 2019; 152(2): 346–352, doi: 10.1016/j.ygyno.2018.11.032, indexed in Pubmed: 30578004.
38. Zhao J, Liu J, Chen K, et al. What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. Breast Cancer Res Treat. 2014; 145(1): 113–128, doi: 10.1007/s10549-014-2914-x, indexed in Pubmed: 24671358.
39. Anderson RA, Mansi J, Coleman RE, et al. The utility of anti-Müllerian hormone in the diagnosis and prediction of loss of ovarian function following chemotherapy for early breast cancer. Eur J Cancer. 2017; 87: 58–64, doi: 10.1016/j.ejca.2017.10.001, indexed in Pubmed: 29117576.
40. Mourits MJ, de Vries EG, Willemse PH, et al. Ovarian cysts in women receiving tamoxifen for breast cancer. Br J Cancer. 1999; 79(11-12): 1761–1764, doi: 10.1038/sj.bjc.6690280, indexed in Pubmed: 10206289.
41. Braems G, Denys H, De Wever O, et al. Use of tamoxifen before and during pregnancy. Oncologist. 2011; 16(11): 1547–1551, doi: 10.1634/theoncologist.2011-0121, indexed in Pubmed: 22020212.
42. Schuurman TN, Witteveen PO, van der Wall E, et al. Tamoxifen and pregnancy: an absolute contraindication? Breast Cancer Res Treat. 2019; 175(1): 17–25, doi: 10.1007/s10549-019-05154-7, indexed in Pubmed: 30707336.
43. Buonomo B, Brunello A, Noli S, et al. Tamoxifen Exposure during Pregnancy: A Systematic Review and Three More Cases. Breast Care (Basel). 2020; 15(2): 148–156, doi: 10.1159/000501473, indexed in Pubmed: 32398983.
44. Bellet M, Gray KP, Francis PA, et al. Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy. J Clin Oncol. 2016; 34(14): 1584–1593, doi: 10.1200/JCO.2015.61.2259, indexed in Pubmed: 26729437.
45. Bernhard J, Zahrieh D, Castiglione-Gertsch M, et al. International Breast Cancer Study Group Trial VIII. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients--the International Breast Cancer Study Group Trial VIII. J Clin Oncol. 2007; 25(3): 263–270, doi: 10.1200/JCO.2005.04.5393, indexed in Pubmed: 17159194.
46. Partridge AH, Niman SM, Ruggeri M, et al. International Breast Cancer Study Group, POSITIVE Trial Collaborators. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. N Engl J Med. 2023; 388(18): 1645–1656, doi: 10.1056/NEJMoa2212856, indexed in Pubmed: 37133584.
47. Lambertini M, Martel S, Campbell C, et al. Pregnancies during and after trastuzumab and/or lapatinib in patients with human epidermal growth factor receptor 2-positive early breast cancer: Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer. 2019; 125(2): 307–316, doi: 10.1002/cncr.31784, indexed in Pubmed: 30335191.
48. Ruddy KJ, Guo H, Barry W, et al. Chemotherapy-related amenorrhea after adjuvant paclitaxel-trastuzumab (APT trial). Breast Cancer Res Treat. 2015; 151(3): 589–596, doi: 10.1007/s10549-015-3426-z, indexed in Pubmed: 25981899.
49. Ruddy KJ, Zheng Y, Tayob N, et al. Chemotherapy-related amenorrhea (CRA) after adjuvant ado-trastuzumab emtansine (T-DM1) compared to paclitaxel in combination with trastuzumab (TH) (TBCRC033:

ATEMPT Trial). Breast Cancer Res Treat. 2021; 189(1): 103–110, doi: 10.1007/s10549-021-06267-8, indexed in Pubmed: 34120223.
50. Hassel JC, Livingstone E, Allam JP, et al. Fertility preservation and management of pregnancy in melanoma patients requiring systemic therapy. ESMO Open. 2021; 6(5): 100248, doi: 10.1016/j.esmoop.2021.100248, indexed in Pubmed: 34438241.
51. Rambhatla A, Strug MR, De Paredes JG, et al. Fertility considerations in targeted biologic therapy with tyrosine kinase inhibitors: a review. J Assist Reprod Genet. 2021; 38(8): 1897–1908, doi: 10.1007/s10815-021-02181-6, indexed in Pubmed: 33826052.
52. Clement SC, Peeters RP, Ronckers CM, et al. Intermediate and long--term adverse effects of radioiodine therapy for differentiated thyroid carcinoma--a systematic review. Cancer Treat Rev. 2015; 41(10): 925––934, doi: 10.1016/j.ctrv.2015.09.001, indexed in Pubmed: 26421813.
53. Evranos B, Faki S, Polat SB, et al. Effects of Radioactive Iodine Therapy on Ovarian Reserve: A Prospective Pilot Study. Thyroid. 2018; 28(12): 1702–1707, doi: 10.1089/thy.2018.0129, indexed in Pubmed: 30156472.
54. Garutti M, Lambertini M, Puglisi F. Checkpoint inhibitors, fertility, pregnancy, and sexual life: a systematic review. ESMO Open. 2021; 6(5): 100276, doi: 10.1016/j.esmoop.2021.100276, indexed in Pubmed: 34597942.
55. Salzmann M, Tosev G, Heck M, et al. Male fertility during and after immune checkpoint inhibitor therapy: A cross-sectional pilot study. Eur J Cancer. 2021; 152: 41–48, doi: 10.1016/j.ejca.2021.04.031, indexed in Pubmed: 34062486.
56. Lambertini M, Horicks F, Del Mastro L, et al. Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: From biological evidence to clinical application. Cancer Treat Rev. 2019; 72: 65–77, doi: 10.1016/j.ctrv.2018.11.006, indexed in Pubmed: 30530271.
57. Sofiyeva N, Siepmann T, Barlinn K, et al. Gonadotropin-Releasing Hormone Analogs for Gonadal Protection During Gonadotoxic Chemotherapy: A Systematic Review and Meta-Analysis. Reprod Sci. 2019; 26(7): 939––953, doi: 10.1177/1933719118799203, indexed in Pubmed: 30270741.
58. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2018; 36(19): 1981–1990, doi: 10.1200/JCO.2018.78.0858, indexed in Pubmed: 29718793.
59. Senra JC, Roque M, Talim MCT, et al. Gonadotropin-releasing hormone agonists for ovarian protection during cancer chemotherapy: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018; 51(1): 77–86, doi: 10.1002/uog.18934, indexed in Pubmed: 29055060.
60. GILANI M, HASANZADEH M, GHAEMMAGHAMI F, et al. Ovarian preservation with gonadotropin-releasing hormone analog during chemotherapy. Asia Pac J Clin Oncol. 2007; 3(2): 79–83, doi: 10.1111/j.1743--7563.2007.00089.x.
61. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019; 112(6): 1022–1033, doi: 10.1016/j.fertnstert.2019.09.013, indexed in Pubmed: 31843073.
62. Dohle GR. Male infertility in cancer patients: Review of the literature. Int J Urol. 2010; 17(4): 327–331, doi: 10.1111/j.1442-2042.2010.02484.x, indexed in Pubmed: 20202000.
63. Delessard M, Saulnier J, Rives A, et al. Exposure to Chemotherapy During Childhood or Adulthood and Consequences on Spermatogenesis and Male Fertility. Int J Mol Sci. 2020; 21(4), doi: 10.3390/ijms21041454, indexed in Pubmed: 32093393.
64. Santaballa A, Márquez-Vega C, Rodríguez-Lescure Á, et al. Multidisciplinary consensus on the criteria for fertility preservation in cancer patients. Clin Transl Oncol. 2022; 24(2): 227–243, doi: 10.1007/s12094-021-02699-2, indexed in Pubmed: 34635959.
65. Oktay K, Harvey BE, Partridge AH, et al. Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018; 36(19): 1994–2001, doi: 10.1200/JCO.2018.78.1914, indexed in Pubmed: 29620997.
66. Jedrzejczak P, Taszarek-Hauke G, Korman M, et al. [The sperm quality in young patients before cancer therapy]. Przegl Lek. 2004; 61(3): 141–145, indexed in Pubmed: 15518321.
67. Brannigan RE, Fantus RJ, Halpern JA. Fertility preservation in men: a contemporary overview and a look toward emerging technologies. Fertil Steril. 2021; 115(5): 1126–1139, doi: 10.1016/j.fertnstert.2021.03.026, indexed in Pubmed: 33933174.
68. Tur-Kaspa I, Segal S, Moffa F, et al. Viagra for temporary erectile dysfunction during treatments with assisted reproductive technologies. Hum Reprod. 1999; 14(7): 1783–1784, doi: 10.1093/humrep/14.7.1783, indexed in Pubmed: 10402389.
69. Mehta A, Sigman M. Management of the dry ejaculate: a systematic review of aspermia and retrograde ejaculation. Fertil Steril. 2015; 104(5): 1074–1081, doi: 10.1016/j.fertnstert.2015.09.024, indexed in Pubmed: 26432530.
70. Meng X, Fan L, Wang T, et al. Electroejaculation combined with assisted reproductive technology in psychogenic anejaculation patients refractory to penile vibratory stimulation. Transl Androl Urol. 2018; 7(Suppl 1): S17–S22, doi: 10.21037/tau.2018.01.15, indexed in Pubmed: 29644166.
71. Ohl DA, Quallich SA, Sønksen J, et al. Anejaculation and retrograde ejaculation. Urol Clin North Am. 2008; 35(2): 211–20, viii, doi: 10.1016/j.ucl.2008.01.014, indexed in Pubmed: 18423241.
72. Furuhashi K, Ishikawa T, Hashimoto H, et al. Onco-testicular sperm extraction: testicular sperm extraction in azoospermic and very severely oligozoospermic cancer patients. Andrologia. 2013; 45(2): 107–110, doi: 10.1111/j.1439-0272.2012.01319.x, indexed in Pubmed: 22690948.
73. Grin L, Girsh E, Harlev A. Male fertility preservation-Methods, indications and challenges. Andrologia. 2021; 53(2): e13635, doi: 10.1111/and.13635, indexed in Pubmed: 32390180.
74. Del-Pozo-Lérida S, Salvador C, Martínez-Soler F, et al. Preservation of fertility in patients with cancer (Review). Oncol Rep. 2019; 41(5): 2607–2614, doi: 10.3892/or.2019.7063, indexed in Pubmed: 30896846.
75. Dolmans MM, Marinescu C, Saussoy P, et al. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood. 2010; 116(16): 2908–2914, doi: 10.1182/blood-2010-01-265751, indexed in Pubmed: 20595517.
76. De Rycke M, Belva F, Goossens V, et al. ESHRE PGD Consortium data collection XIII: cycles from January to December 2010 with pregnancy follow-up to October 2011. Hum Reprod. 2015; 30(8): 1763–1789, doi: 10.1093/humrep/dev122, indexed in Pubmed: 26071418.
77. Ethics Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org, Ethics Committee of the American Society for Reproductive Medicine. Use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions: an Ethics Committee opinion. Fertil Steril. 2018; 109(6): 989–992, doi: 10.1016/j.fertnstert.2018.04.003, indexed in Pubmed: 29935659.
78. Practice Committee of Society for Assisted Reproductive Technology, Practice Committee of American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice Committee opinion. Fertil Steril. 2008; 90(5 Suppl): S136–S143, doi: 10.1016/j.fertnstert.2008.08.062, indexed in Pubmed: 19007612.
79. Ustawa z dnia 25 czerwca 2015 roku o leczeniu niepłodności, Dz. U. 2020 poz. 442 t.j.
80. Haberko J. Komentarz do ustawy o leczeniu niepłodności. https://sip.lex.pl/komentarze-i-publikacje/komentarze/ustawa-o-leczeniu--nieplodnosci-komentarz-587696505 (30.03.2023).
81. Ustawa z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty, Dz. U. 2021 poz. 790 t.j.
82. Kanafek K. Rozwodowa niezgoda – dysponowanie niewykorzystanymi embrionami. Internetowy Przegląd Prawniczy. 2017; 2: 62.
83. Speller B, Sissons A, Daly C, et al. An evaluation of oncofertility decision support resources among breast cancer patients and health care providers. BMC Health Serv Res. 2019; 19(1): 101, doi: 10.1186/s12913-019-3901-z, indexed in Pubmed: 30728004.
84. Gardino SL, Jeruss JS, Woodruff TK. Using decision trees to enhance interdisciplinary team work: the case of oncofertility. J Assist Reprod Genet. 2010; 27(5): 227–231, doi: 10.1007/s10815-010-9413-8, indexed in Pubmed: 20386978.
85. van der Kooi ALLF, Kelsey TW, van den Heuvel-Eibrink MM, et al. Perinatal complications in female survivors of cancer: a systematic review and meta-analysis. Eur J Cancer. 2019; 111: 126–137, doi: 10.1016/j.ejca.2019.01.104, indexed in Pubmed: 30849686.
86. Buonomo B, Brunello A, Noli S, et al. Tamoxifen Exposure during Pregnancy: A Systematic Review and Three More Cases. Breast Care (Basel). 2020; 15(2): 148–156, doi: 10.1159/000501473, indexed in Pubmed: 32398983.
87. Partridge AH, Pagani O, Niman SM, et al. Pregnancy outcomes and safety of interrupting therapy for women with endocrine responsive breast cancer: Primary results from the POSITIVE trial (IBCSG 48-14/BIG 8-13). Presented at SABCS 2022. December 6-10, 2022. Abstract GS4-09.
88. Pereg D, Koren G, Lishner M. Cancer in pregnancy: gaps, challenges and solutions. Cancer Treat Rev. 2008; 34(4): 302–312, doi: 10.1016/j.ctrv.2008.01.002, indexed in Pubmed: 18291591.
89. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. Lancet Oncol. 2004; 5(5): 283–291, doi: 10.1016/S1470-2045(04)01466-4, indexed in Pubmed: 15120665.

90. Nicholson HO. Cytotoxic drugs in pregnancy. Review of reported cases. J Obstet Gynaecol Br Commonw. 1968; 75(3): 307–312, doi: 10.1111/j.1471-0528.1968.tb02083.x, indexed in Pubmed: 4868587.
91. Esposito S, Tenconi R, Preti V, et al. Chemotherapy against cancer during pregnancy: A systematic review on neonatal outcomes. Medicine (Baltimore). 2016; 95(38): e4899, doi: 10.1097/MD.0000000000004899, indexed in Pubmed: 27661036.
92. Avilés A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. Clin Lymphoma. 2001; 2(3): 173–177, doi: 10.3816/clm.2001.n.023, indexed in Pubmed: 11779294.
93. Amant F, Van Calsteren K, Halaska MJ, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol. 2012; 13(3): 256–264, doi: 10.1016/S1470-2045(11)70363-1, indexed in Pubmed: 22326925.
94. Vandenbroucke T, Verheecke M, van Gerwen M, et al. International Network on Cancer, Infertility and Pregnancy (INCIP). Child development at 6 years after maternal cancer diagnosis and treatment during pregnancy. Eur J Cancer. 2020; 138: 57–67, doi: 10.1016/j.ejca.2020.07.004, indexed in Pubmed: 32858478.

VIA MEDICA

ORIGINAL ARTICLE

Barbara Radecka[1, 2], Joanna Hudała-Klecha[1, 2], Dariusz Sawka[3], Jolanta Sarga[2], Bożena Noworolska[2], Grażyna Susczyk[2], Jolanta Sawicka[3], Elżbieta Duda[2], Natalia Obruśnik[2], Patryk Zając[2, 4]

[1]Department of Oncology, Institute of Medical Sciences, University of Opole, Poland
[2]Oncology Clinic with Daily Ward, Opole Oncology Center of Prof. Tadeusz Koszarowski, Poland
[3]B. Markiewicz Specialist Hospital of the Podkarpacki Oncological Center, Brzozów, Poland
[4]Department of Clinical Biochemistry and Laboratory Diagnostics, Institute of Medical Sciences, University of Opole, Poland

Home-based treatment with subcutaneous trastuzumab: safe and acceptable not only during a pandemic — final analysis of the RWD project 'FlexCare'

Address for correspondence:
Assoc. Prof. Barbara Radecka MD, PhD
Department of Clinical Oncology,
Tadeusz Koszarowski Cancer Center
in Opole
ul. Katowicka 66a, 45–061 Opole, Poland
e-mail: barbara.s.radecka@gmail.com

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice
DOI: 10.5603/OCP.2023.0025

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. Trastuzumab shows similar efficacy and safety profile regardless of IV or SC administration. Subcutaneous administration enables reduction of treatment costs and time as well as equipment savings and is more convenient for both patients and healthcare providers. In Poland, home-based programs of treatment with biological drugs are already implemented; however, to date they do not include trastuzumab in BC patients. The project aimed to evaluate the organizational and therapeutic procedures related to home-based treatment with subcutaneous trastuzumab and satisfaction of patients and healthcare providers based on RWE.

Material and methods. Early HER2(+) BC patients treated with trastuzumab were enrolled in the study. Monitoring and duration of treatment were consistent with the summary of product characteristics (SmPC) and reimbursement rules. The first 3–6 doses of trastuzumab were administered at the cancer center, followed by home doses. Medical visits took place every 3 months. The data were analyzed using descriptive statistics. A positive opinion of the Bioethics Committee was obtained.

Results. Twenty patients participated in the project. The median age was 59 years (36–72 years). The average distance from the place of residence to the hospital was 24 km (2–65 km). We administered 232 doses, with an average of 11.6 doses per patient (range 6–14). The tolerance of trastuzumab was good and consistent with the SmPC. The average duration of a nurse's stay at home was 60 minutes. Almost all patients (19/20) appreciated the possibility of saving time and continuing their professional work as well as avoiding crowds and the risk of infection in the hospital. Two patients felt that nurse visits violated their privacy. No logistical or technical problems were observed.

Conclusions. Home-based treatment with subcutaneously administered trastuzumab is safe and easy to organize, positively perceived by both patients and nurses. It can be particularly important for disabled patients who have difficulty reaching the hospital, as well as for professionally active patients.

Keywords: trastuzumab, subcutaneous use, home-based treatment, breast cancer

Oncol Clin Pract 2024; 20, 2: 117–123

Received: 04.05.2023 Accepted: 04.05.2023 Early publication date: 10.07.2023

Introduction

HER2-positive (HER2+) disease accounts for 15–20% of all breast cancers and is characterized by overexpression of the human epidermal growth factor receptor type 2 (HER2) and/or amplification of the coding gene [1]. Positive HER2 expression is a prognostic factor (associated with a worse prognosis) as well as a predictive factor — drugs that inhibit the HER2 signaling pathway have been developed [2]. The first drug that significantly improved the treatment outcomes in patients with HER2-positive breast cancer was trastuzumab [recombinant humanized IgG1 (immunoglobulin IgG1) monoclonal antibody binding to the extracellular domain of the HER2 receptor] [3]. Since its discovery at the end of the 20th century, other drugs have been developed that target the HER2 signaling pathway. The ones that are currently available include small-molecule tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib), another monoclonal antibody (pertuzumab), and conjugates of antibodies and cytotoxic drugs (trastuzumab emtansine, trastuzumab deruxtecan, trastuzumab duocarmazine) [4–10]. Further drugs are the subject of ongoing clinical trials, which are in various phases.

The current standard of adjuvant systemic treatment in patients with early HER2-positive breast cancer includes the use of chemotherapy in combination with biological therapies targeting HER2 receptors. Biological treatment includes one year of trastuzumab, and in selected clinical cases, additionally pertuzumab and trastuzumab emtansine in patients with residual disease [11–13]. Compared to chemotherapy alone, this therapy significantly reduces the risk of disease recurrence and death and is in line with the guidelines of scientific societies [14].

Trastuzumab can be used in the intravenous form (infusion lasting 30–90 minutes) as the original drug (Herceptin®) or biosimilars, and in the subcutaneous form (injection 2–5 minutes), available only as the original preparation (Herceptin SC®). In a multicenter open-label randomized non-inferiority phase III clinical trial, no differences regarding efficacy and safety profile were found between these two forms of drug administration [15, 16]. On the other hand, a benefit was demonstrated in terms of reduction of treatment costs, saving time and equipment, as well as human resources when using the subcutaneous form compared to the intravenous form [17, 18]. The subcutaneous form is preferred by patients and medical staff as a more patient-friendly treatment, and it significantly shortens the patient's stay in the outpatient clinic or hospital [19].

The subcutaneous form of the drug in disposable applicators self-injected by the patient was also evaluated. Due to the costs of production and disposal, applicators were not used in everyday practice, but they were very positively assessed by patients and staff [20].

Subcutaneous trastuzumab may also be an attractive drug for home administration. In recent years, there has been a systematically increasing interest in the use of various forms of anticancer treatment at the patient's home (including oral and intravenous chemotherapy administered with the use of infusors), which improves patients' comfort, saves time and medical staff resources, and reduces the burden on the medical facilities [21–23]. Legal regulations in this area are being extended. The pandemic has highlighted the need for more flexible forms of treatment that can also be cost-effective and has accelerated their implementation. In Poland, trastuzumab has not been administered in everyday practice at home so far, although this form of treatment is used worldwide [24].

Aim of study

The FlexCare project aimed to collect information and evaluate organizational procedures during treatment with subcutaneous trastuzumab at home and in the treatment room (as part of nursing advice) and to assess patients and staff's satisfaction and sense of security.

Material and methods

The project was conducted in two comprehensive cancer centers in Poland, the Opole Oncology Center in Opole and the Podkarpacki Oncological Center in Brzozów, during the COVID-19 pandemic from December 2020 to December 2021. The inclusion criteria included

- written informed consent;
- age > 18 years;
- meeting the inclusion criteria for treatment in the drug program B.9 (PL B.9) in the version applicable during the project;
- adjuvant treatment with subcutaneous trastuzumab in monotherapy (after prior administration of the drug in combination with chemotherapy);
- absence of serious concomitant diseases;
- normal bone marrow, kidney, and heart function [left ventricular ejection fraction (LVEF) ≥ 50% in accordance with the requirements of the drug program];
- at least 3 drug administrations so far;
- no significant trastuzumab-related adverse events so far.

The treatment was conducted in accordance with the SmPC of the originator medicine. Eligibility for treatment, monitoring, and treatment duration were in line with PL B.9. The first 3–6 doses of the drug were administered in an oncology center in stationary or daily care mode. During the project, Herceptin SC® was administered at the patient's home or in the treatment

Figure 1. Nursing kit

room, and stationary medical visits took place on the day of scheduled monitoring visits (including laboratory and cardiological tests following PL B.9. treatment monitoring recommendations) and in every medically justified situation. Both in the case of administration at home and in the treatment room, a doctor (researcher) conducted a teleconsultation.

Trastuzumab was administered by a qualified nurse experienced in using the drug and trained in the management of allergic reactions. The nurse transported trastuzumab in a cooler bag and was equipped with a basic set of drugs to be used in the case of a hypersensitivity reaction and a set for medical waste disposal (Fig. 1). The assessment of the patient's condition before drug administration was conducted by the nurse according to a prepared questionnaire (taking medical history regarding well-being and measurements of basic vital signs). The course of the visit (interview, drug administration, post-injection observation) was reported by the nurse in appropriate questionnaires and communicated to the doctor over the phone. The time of patient observation after drug administration was intended for an educational talk.

Data were analyzed using descriptive statistics. Quantitative variables were expressed as mean, median, and range, and qualitative variables as sample numbers and percentages.

A positive opinion of the Bioethics Committee at the Opole Medical Chamber was obtained, as well as financial support from Roche, which provided the study drug free of charge.

Results

The project involved 20 female patients diagnosed with HER2+ early breast cancer. Four patients who were offered participation in the project declined (one due to concerns about the safety of the procedure and the others due to privacy concerns).

The median age of patients was 59 years (range 36–72 years). Seven women (35%) were professionally active, but as many as 50% were in pre-retirement age.

The average distance from the place of residence to the hospital was 24 km (range 2–65 km). All patients cooperated, were in proper contact, and, in their self-assessment, were independent in everyday activities. Only one patient reported mobility limitations due to degenerative joint disease.

A total of 232 doses were administered, corresponding to 11.6 doses per patient (range 6–14 doses). The majority of applications (57%) took place at home (Tab. 1).

The overall tolerability of trastuzumab was good and consistent with the SmPC. One patient (5%) discontinued therapy prematurely due to a decrease in left ventricular ejection fraction, and the remaining patients completed treatment as planned. All patients completed a satisfaction questionnaire. Almost all (95%) appreciated saving time, the ability to continue working, avoiding hospital crowds and the risk of infection. Almost all patients (90%) would recommend a home-based form of drug administration, but every tenth considered that the nurse's visit disturbed their privacy. No patient reported negative opinions, even though such a possibility was included in the questionnaires (I feel isolated/lonely with my disease; I am afraid of complications and that something will happen; it interferes with my privacy; there is no doctor nearby who gives me a sense of security). The patients also positively assessed drug administration in the treatment room combined with nursing advice. They emphasized a significantly shorter stay in the facilities compared to standard medical visits. One patient preferred administration in the treatment room but did not justify her choice, and the remaining patients preferred administration at home.

Three nurses participated in the project. The median subcutaneous injection time was 4 minutes (range 3–6), and the nurses' home visits lasted 55 minutes (range 30–130 minutes). Logistical and technical problems were not observed. Twice a nurse was waiting for the patient. Mild pain was reported during 12/232 applications (5%), and redness at the application site was observed after 9/232 applications (4%). Side effects did not extend the injection time and did not stop subsequent home administrations.

The nurses emphasized the value of health education of patients during these visits (maintaining proper body weight, regular physical activity, and not

Table 1. Number of trastuzumab administrations

	Number of administrations	At home	In the office
Total	232	133	99
Per person	11.6	6.65	4.95

using stimulants). The nurses emphasized the benefits for the treated women, mainly saving time and reducing the risk of infections. However, they noted the excessive amount of medical documentation that needed to be completed during home visits. The nurses highly appreciated the implementation of treatment in the nursing office and giving advice, which was a source of novel learning and experience as well as professional prestige for them.

Discussion

Self-administration of subcutaneous biologics is a common procedure in patients with diabetes, rheumatoid arthritis (RA), multiple sclerosis, and hemophilia [25]. The concept of home-based cancer treatment is also not new. Several studies have evaluated the possibility of administering cytotoxic and biological drugs at home [26–28].

In Poland, there are home-use programs for biological drugs. An example is the treatment of RA patients with tocilizumab [29]. Tocilizumab, a humanized IgG1 monoclonal antibody directed against the human interleukin 6 (IL-6) receptor, is administered subcutaneously using a single-use pre-filled syringe and a safety needle. A doctor starts the treatment. After appropriate instruction, the patient performs the first injection under the supervision of qualified medical staff, and the next injection can be performed independently at home. The patient's parent/guardian can also do this. The drug is administered weekly, and the patient reports every 3 months (with drug packages) for monitoring visits, during which the effectiveness and tolerability of treatment are assessed.

As part of the National Hemophilia Treatment Program, it is possible to self-administer at home emicizumab, a humanized monoclonal antibody, as a prophylaxis of bleeding episodes in patients with hemophilia A [30]. Before starting emicizumab, the patient is educated by the attending physician on the rules of drug taking (including injecting the precisely calculated dose and adherence to the injection timing regime, as well as potential side effects associated with the use of emicizumab and interactions with other drugs). The patient collects the drug, administers it subcutaneously at home and brings the used packaging to the treatment center.

To our knowledge, FlexCare is the first project in Poland to assess the possibility of home treatment with subcutaneous trastuzumab. The results of the FlexCare study highlight the benefits for patients and nurses in the subcutaneous use of the drug. Since each patient had previously received several doses of the drug in the hospital during a one-day stay, they could compare both procedures. Home administrations were quick, taking less than 5 minutes in most cases, with the entire procedure taking less than an hour. Few side effects were observed, and almost all patients would recommend this form of treatment. The nurses reported that organizational problems were rare, and visits provided professional satisfaction. The reported side effects were minor, did not extend the duration of injection, and did not result in excluding patients from the project. The nurses reported more adverse events than patients — perhaps because of the severity of the disease, adverse events were less important for the patients than for the nurses, and because the patients had become accustomed to pain during treatment [31]. Detailed analysis of the results (data not included) showed no difference in the perception of side effects depending on the number of injections given at home.

No organizational problems were observed during the project. The cold chain was preserved, and the importance of proper storage of biological drugs and the creation of conditions identical to those existing in oncology centers should be emphasized. Only three nurses participated in the project, which probably facilitated quality control and adherence to procedures.

The follow-up time after drug administration was respected. During the project, a post-authorization change to the SmPC of the original drug was made — the observation time after drug administration was reduced from 120 to 30 minutes, which was also introduced in the FlexCare project.

The FlexCare project was an example of the growing popularity of initiatives that reduce the burden of patients traveling to cancer centers. Moving treatment closer to patients or even to their homes by setting up satellite centers or mobile offices increases the possibilities of therapy and is accepted. This project also showed that anti-cancer biological treatment could be partially implemented by qualified nursing staff. Data from clinical trials show that, compared to intravenous administration, subcutaneous trastuzumab is preferred by patients, saves time for medical staff, shortens the time of drug preparation and administration, and reduces direct and indirect costs [19]. In this context, trastuzumab is well suited for implementation in various flexible forms of care.

In the Belgian BELIS study, a similar treatment plan was implemented — trastuzumab was administered intravenously in a daily ward, then subcutaneously in a day hospital, and finally subcutaneously at home [32]. The results of this study show that home use of trastuzumab is feasible and preferred by patients. In numerous programs and pilot studies in Europe, it was found that subcutaneous trastuzumab can be safely used at home, in primary care facilities, or local hospitals [31, 33–36]. These programs require planning, training, careful selection of patients, and good cooperation of medical staff at various levels as well as the creation of remote care systems. They can lead to an improvement in the quality of life of patients and reduce the financial burden on the system. The concepts of flexible care turned out to be particularly important during the COVID-19 pandemic, but it is worth implementing them regardless of the epidemic situation.

In recent years, a subcutaneous form of a combination preparation — trastuzumab and pertuzumab — has been approved for marketing. A phase III study confirmed its efficacy, safety, and pharmacokinetics compared with separately administered intravenous forms of both antibodies [37]. Patients also prefer the subcutaneous preparation of both drugs [38]. A study is currently underway in the United States evaluating home treatment with subcutaneous trastuzumab and pertuzumab [28]. There are also studies evaluating subcutaneous forms of other anti-cancer biological drugs.

The discussed project confirms the feasibility of implementing subcutaneous trastuzumab treatment at home. It is possible to conduct this medical procedure as part of standard oncological care. The treatment is safe and allows for a high level of patient and staff satisfaction. It helps patients to maintain professional activity and can be extremely valuable in the case of patients with limited mobility, for whom access to the treatment center is an insurmountable obstacle. The development of the discussed procedure should be considered as an additional form of treatment for patients with HER2-positive breast cancer. In our opinion, it would be a very valuable alternative. The project also showed that the standard course of treatment recommended by an oncologist could be performed independently by qualified nurses. We think that further organizational steps are possible to introduce nursing advice in oncology and implement selected procedures by qualified oncology nurses (closer to the patient's place of residence) after prior patient qualification by the oncologist in charge.

The strength of this study is its prospective nature, while the limitation — the small number of patients, implementation in only two centers, and the declarative nature of data collection. It would, therefore, be interesting to extend the project to other centers and include patients with advanced disease.

Treatment of breast cancer patients with trastuzumab has a long history. The side effect profile is well known and described. Making treatment delivery more flexible represents progress and may benefit the system.

Conclusions

Subcutaneous use of trastuzumab at home is safe and easy to organize and well-received by patients and staff. This form of treatment organization should be popularized, as it helps to free up hospital resources. It can be valuable for disabled patients with limited access to hospitals and for professionally active people. An educated nurse can conduct part of the chronic treatment with trastuzumab independently, relieving the doctor's workload. Real-world data can help to introduce this additional care option.

Article Information and Declarations

Data availability statement

All analyzed data is included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement

A positive opinion was obtained from the Bioethics Committee at the Opole Medical Chamber in Opole.

Author contributions

B.R.: should be considered the major author; author of the concept, methods, research (treatment and follow-up of the patients), data analysis, manuscript preparation; J.H.-K.: author of the concept, methods, research (treatment and follow-up of the patients), manuscript preparation; D.S., J.Sarga, B.N., G.S., J.Sawicka: treatment and follow-up of the patients; E.D.: author of the concept, methods; N.O.: follow-up of the patients, data analysis; P.Z.: follow-up of the patients, data analysis, manuscript preparation.

Funding

Financial support was obtained from Roche, which provided the drug for administration within the project free of charge.

Acknowledgments

The authors express their great thanks to the patients who decided to participate in the project.

Conflict of interest

B.R.: received honoraria from Amgen, AstraZeneca, BMS, Gilead, Lilly, Novartis, Pfizer, Pierre-Fabre, Roche, Servier unrelated to the article.
J.H.-K.: received honoraria from: Lilly, Novartis, Roche unrelated to the article.
Other autors declare no conflict of interest.

References

1. Zhang D, Salto-Tellez M, Do E, et al. Evaluation of HER-2/neu oncogene status in breast tumors on tissue microarrays. Hum Pathol. 2003; 34(4): 362–368, doi: 10.1053/hupa.2003.60, indexed in Pubmed: 12733117.
2. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235(4785): 177–182, doi: 10.1126/science.3798106, indexed in Pubmed: 3798106.
3. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344(11): 783–792, doi: 10.1056/NEJM200103153441101, indexed in Pubmed: 11248153.
4. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012; 30(21): 2585–2592, doi: 10.1200/JCO.2011.35.6725, indexed in Pubmed: 22689807.
5. Martin M, Holmes F, Ejlertsen B, et al. ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017; 18: 1688–1700.
6. Murthy R, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020; 382(6): 586–586, doi: 10.1056/nejmx190039.
7. Baselga J, Cortés J, Im SA, et al. CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366(2): 109–119, doi: 10.1056/NEJMoa1113216, indexed in Pubmed: 22149875.
8. Swain SM, Miles D, Kim SB, et al. CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020; 21(4): 519–530, doi: 10.1016/S1470-2045(19)30863-0, indexed in Pubmed: 32171426.
9. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N Engl J Med. 2012; 367(19): 1783–1791, doi: 10.1056/nejmoa1209124.
10. Modi S, Saura C, Yamashita T, et al. DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020; 382(7): 610–621, doi: 10.1056/NEJMoa1914510, indexed in Pubmed: 31825192.
11. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. Herceptin Adjuvant (HERA) Trial Study Team. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017; 389(10075): 1195–1205, doi: 10.1016/S0140-6736(16)32616-2, indexed in Pubmed: 28215665.
12. Piccart M, Procter M, Fumagalli D, et al. APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021; 39(13): 1448–1457, doi: 10.1200/JCO.20.01204, indexed in Pubmed: 33539215.
13. Minckwitz Gv, Huang CS, Mano M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019; 380(7): 617–628, doi: 10.1056/nejmoa1814017.
14. Radecka B. Trastuzumab as adjuvant treatment for early stage HER2-positive breast cancer — a 10 year history. Nowotwory. Journal of Oncology. 2017; 66(6): 477–485, doi: 10.5603/njo.2016.0085.
15. Ismael G, Hegg R, Muehlbauer S, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol. 2012; 13(9): 869–878, doi: 10.1016/S1470-2045(12)70329-7, indexed in Pubmed: 22884505.
16. Jackisch C, Kim SB, Semiglazov V, et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. Ann Oncol. 2015; 26(2): 320–325, doi: 10.1093/annonc/mdu524, indexed in Pubmed: 25403587.
17. Burcombe R, Chan S, Simcock R, et al. Subcutaneous trastuzumab (Herceptin®): A UK time and motion study in comparison with intravenous formulation for the treatment of patients with HER2-positive early breast cancer. Adv Breast Cancer Res. 2013; 2: 133–140.
18. Hedayati E, Fracheboud L, Srikant V, et al. Economic benefits of subcutaneous trastuzumab administration: A single institutional study from Karolinska University Hospital in Sweden. PLoS One. 2019; 14(2): e0211783, doi: 10.1371/journal.pone.0211783, indexed in Pubmed: 30716137.
19. Pivot X, Verma S, Fallowfield L, et al. PrefHer Study Group, PrefHer Study Group, PrefHer Study Group. Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study. Lancet Oncol. 2013; 14(10): 962–970, doi: 10.1016/S1470-2045(13)70383-8, indexed in Pubmed: 23965225.
20. Gligorov J, Ataseven B, Verrill M, et al. SafeHer Study Group. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. Eur J Cancer. 2017; 82: 237–246, doi: 10.1016/j.ejca.2017.05.010, indexed in Pubmed: 28625777.
21. Bordonaro S, Raiti F, Di Mari A, et al. Active home-based cancer treatment. J Multidiscip Healthc. 2012; 5: 137–143, doi: 10.2147/JMDH.S31494, indexed in Pubmed: 22807631.
22. Mitchell T. Patients' experiences of receiving chemotherapy in outpatient clinic and/or onboard a unique nurse-led mobile chemotherapy unit: a qualitative study. Eur J Cancer Care (Engl). 2013; 22(4): 430–439, doi: 10.1111/ecc.12044, indexed in Pubmed: 23611562.
23. Wyrwicz L. Innowacje w leczeniu systemowym raka jelita grubego. In: Więckowska B, Maciejczyk A. ed. Innowacyjna onkologia: potrzeby, możliwości, system. PZWL Wydawnictwo Lekarskie, Warszawa 2020: 178.
24. Battisti N, Lee KA, Nash T, et al. 222P Rates of cardiac adverse events in older versus younger adults receiving trastuzumab for HER2-positive early breast cancer: Results from 931 patients treated at The Royal Marsden. Ann Oncol. 2020; 31: S330, doi: 10.1016/j.annonc.2020.08.344.
25. Bittner B, Richter W, Schmidt J. Subcutaneous Administration of Biotherapeutics: An Overview of Current Challenges and Opportunities. BioDrugs. 2018; 32(5): 425–440, doi: 10.1007/s40259-018-0295-0, indexed in Pubmed: 30043229.
26. Anderson H, Addington-Hall JM, Peake MD, et al. Domiciliary chemotherapy with gemcitabine is safe and acceptable to advanced non-small-cell lung cancer patients: results of a feasibility study. Br J Cancer. 2003; 89(12): 2190–2196, doi: 10.1038/sj.bjc.6601420, indexed in Pubmed: 14676793.
27. Lal R, Hillerdal GN, Shah RNH, et al. Home administration of maintenance pemetrexed for patients with advanced non-squamous non-small cell lung cancer: rationale, practicalities and phase II feasibility study design. Health Qual Life Outcomes. 2013; 11(2): 163–160, doi: 10.1186/1477-7525-11-163, indexed in Pubmed: 24090033.
28. An expanded access, single-arm, multicenter study to provide at home subcutaneous administration of pertuzumab and trastuzumab fixed-dose combination (PH FDC SC) for patients with HER2-positive breast cancer during the COVID-19 pandemic. https://clinicaltrials.gov/ct2/show/NCT04395508 (8.04.2023).
29. https://www.roche.pl/content/dam/rochexx/rochepl/roche_poland_rwd/pl_PL/documents/SmPC/roactemra_koncentrat.pdf.
30. https://www.gov.pl/web/zdrowie/narodowy-program-leczenia-chorych-na-hemofilie-i-pokrewne-skazy-krwotoczne-na-lata-2019-2023.
31. Pailler C, Chapot T, Softa S, et al. [Subcutaneous administration of trastuzumab at home: Feedback of patients treated in 2016 by Santé service]. Bull Cancer. 2018; 105(12): 1126–1134, doi: 10.1016/j.bulcan.2018.10.005, indexed in Pubmed: 30466957.
32. Denys H, Martinez-Mena CL, Martens MT, et al. Safety and tolerability of subcutaneous trastuzumab at home administration, results of the phase IIIb open-label BELIS study in HER2-positive early breast cancer. Breast Cancer Res Treat. 2020; 181(1): 97–105, doi: 10.1007/s10549-020-05604-7, indexed in Pubmed: 32240454.
33. Roe H. Impact of Switching from Intravenous to Subcutaneous Trastuzumab in the Management of HER2 Positive Breast Cancer. UKONS Annual Conference 2016; November 11-12, 2016, Brighton.
34. Snell A, Ford M. Assessing the impact of a homecare/mobile chemo-therapy unit co-ordinator using subcutaneous herceptin as an example. UKONS Annual Conference 2016. November 11-12, 2016, Brighton.
35. APM Health Europe. Treating patients at home with subcutaneous injections of Roche's Herceptin Hyclecta saves money [press review]. 2020. https://www.apmhealtheurope.com /freestory/0/67360/treating-patients-at-home-with-subcutaneous-injections-of- roche-s-herceptin-hylecta-saves-money (8.04.2023).

36. Tumore al seno. Al Pascale di Napoli, la terapia arriva al domicilio. La prima volta in Italia. https://informatori.it/flash-news/attualita/tumore-al-seno-al-pascale-di-napoli-la-terapia-arriva-al-domicilio-la-prima-volta-in-italia/ (8.04.2023).
37. Tan AR, Im SA, Mattar A, et al. FeDeriCa study group. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol. 2021; 22(1): 85–97, doi: 10.1016/S1470-2045(20)30536-2, indexed in Pubmed: 33357420.
38. O'Shaughnessy J, Sousa S, Cruz J, et al. 165MO Patient (pt) preference for the pertuzumab-trastuzumab fixed-dose combination for subcutaneous use (PH FDC SC) in HER2-positive early breast cancer (EBC): Primary analysis of the open-label, randomised crossover PHranceSCa study. Ann Oncol. 2020; 31: S306–S307, doi: 10.1016/j.annonc.2020.08.287.

VIA MEDICA

ORIGINAL ARTICLE

Aleksandra Bożyk, Kamila Wojas-Krawczyk, Marcin Nicoś, Paweł Krawczyk

Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland

The effect of different concentrations of anti-PD-1 and anti-PD-L1 antibodies on the activity of immune system cells in patients with non-small cell lung cancer

Address for correspondence:
Aleksandra Bożyk, PhD
Department of Pneumonology,
Oncology and Allergology,
Medical University of Lublin, Poland
e-mail: aleksandra.bozyk@umLub.pl

Oncology in Clinical Practice
DOI: 10.5603/ocp.96792

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. The last century abounded in numerous scientific discoveries that allowed us to understand the operation and functioning of one of the most complex human systems, i.e. the immune system. One of the most important discoveries was the work of Prof. James Alison and Prof. Tasuko Honjo on the development of anti-cancer therapy inhibiting negative immune regulation (PD-1 and CTLA-4 molecules). Knowledge of these molecules' action and their huge role in inhibiting immune system activity, e.g. during cancer growth, created the basis for the development of specific monoclonal antibodies, without which clinicians from many specialties cannot imagine modern cancer therapies. However, side effects of these therapies are still quite troublesome.To minimize them, it would be necessary to reduce the dose while still maintaining the effective level of anticancer activity of immune system cells.

Material and methods. In this study, 24-hour culture of PBMCs isolated from blood and bronchoaspirate with various concentrations of nivolumab or atezolizumab was performed. Expression of the individual activation markers on cultured cells was compared to the expression of these markers on cells not subjected to cell culture.

Results and conclusions. The outcomes of our research may indicate that individualized dosages of anti-PD-1 and anti-PD-L1 antibodies may contribute to the effective activation of immune system cells while minimizing the side effects of the therapy.

Keywords: non-small cell lung cancer, immunotherapy, culture cells

Oncol Clin Pract 2024; 20, 2: 124–135

Introduction

Currently, clinicians dealing with lung cancer patients cannot imagine modern therapies for this disease without the use of immunotherapy. The therapeutic possibilities of lung cancer treatment have been enhanced by the use of anti-PD-1 and anti-PD-L1 monoclonal antibodies that block the inhibition pathway of the immune system. The effectiveness of both groups of antibodies has been demonstrated in numerous clinical trials, which translated into widespreadregistration of immunotherapeutic drugs, not only for indication of lung cancer. However, a large percentage of patients do not respond to anti-PD-L1/ /anti-PD-1 treatment despite the presence of the predictive marker in the form of the PD-L1 molecule on the surface of cancer cells. Due to many mechanisms, cancer cells escape from immune surveillance, and cancer is very efficient in avoiding recognition by the immune system [1–3]. This study sought to elucidate immunological mechanisms of regulation of T lymphocyte activity in patients with non-small cell lung cancer as a result of stimulation with anti-PD-1 or anti-PD-L1 antibodies.

Received: 03.08.2023 Accepted: 29.08.2023 Early publication date: 06.11.2023

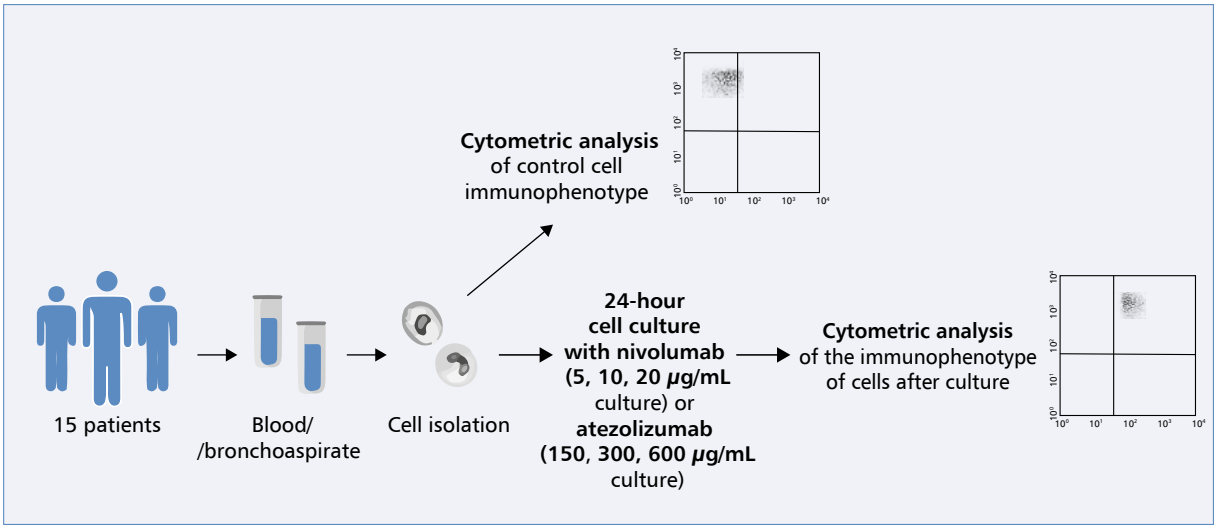

Figure 1. Culture methodology

Material and methods

The study was conducted on a group of 15 patients with locally advanced or advanced lung adenocarcinoma. Six women and 9 men were qualified for the study, with an average age of 66 years. The patients had not previously received any systemic anticancer treatment, antibiotic therapy, drugs stimulating hematopoiesis, or drugs affecting the activity of the immune system; those patients had no diagnosed autoimmune diseases. All investigations were carried out according to relevant guidelines and regulations. Informed consent was obtained from all subjects. The project received a positive opinion from the Bioethics Committee at the Medical University of Lublin (nr KE-0254/318/2018).

Isolation of peripheral blood mononuclear cells

Peripheral blood (9 mL) was collected into Monovette tubes with sodium heparin on the day of the planned bronchoscopy procedure. Bronchoaspirate (15–20 mL) was collected from the patients during bronchoscopy. Only patients diagnosed with lung adenocarcinoma without clinically significant molecular changes were qualified for the first-line anticancer treatment and were included in the final statistical analysis.

Peripheral blood mononuclear cells (PBMC) were generated by layering blood diluted with phosphate-buffered saline (PBS) without calcium and magnesium ions (1:1 ratio) on Lymphoprep. The isolated PBMCs were rinsed twice with a buffered saline solution, counted in a Neubauer chamber, and their viability was assessed using trypan blue. The bronchospirate was filtered through sterile gauze to remove conglomerates of exfoliated epithelial cells and mucus strands. Then, it was centrifuged for 5 min at 2000 rpm.

Conducting short-term cell cultures

The PBMC and bronchoaspirate fraction was cultured for 24 hours in three 6-well plates with RPMI 1640 medium (PAA Laboratories, US) supplemented with antibiotics (1% penicillin-streptomycin-neomycin, Sigma Aldrich, US) at 37°C and 5% CO_2 in different concentrations of nivolumab (5 μg/mL, 10 μg/mL, 20 μg/mL culture) (Bristol-Myers Squibb, US) or atezolizumab (150 μg/mL, 300 μg/mL, 600 μg/mL culture) (Roche, France). Theculture methodology is shown in Figure 1. On the day of completion of the culture, the cells were recovered from the culture well and subjected to immunophenotyping.

The fraction of control cells from peripheral blood and bronchoaspirate, not intended for culture, was aliquoted into cytometric tubes and incubated with a panel of monoclonal antibodies for 30 min. at 4°C. Then, the cells were washed from the remains of unbound antibodies with PBS buffer without Ca^{2+} and Mg^{2+} ions (centrifugation parameters: 2000 rpm/5 min), and detailed analysis of the cell immunophenotype was performed in a flow cytometer.

In turn, cells subjected to short-term culture with individual anti-PD-1 or anti-PD-L1 antibodies, after 24-hour incubation, were incubated with the selected antibodies conjugated with appropriate fluorochromes (anti-CD4-FITC, anti-CD274-FITC, anti-CD14-FITC, anti-CD8-PE, anti-CD14-PE, anti-CD25-APC, anti-CD69-APC, anti-CD95-APC, anti-CD279-APC (Becton Dickinson, US).

Isolated cells from peripheral blood and bronchoaspirate were divided into 2 parts, the first of which was intended for control immunophenotype analysis on the day of material collection (so-called control cells), and the second part was intended for establishing short-term cell cultures.

Results

Evaluation of the percentage of helper and cytotoxic T lymphocytes and monocytes isolated from peripheral blood stimulated with anti-PD-1 antibody compared to unstimulated culture

T helper or T cytotoxic lymphocytes expressed CD25+

In the group of T helper (Th) lymphocytes, we observed a significant increase in the culture with the addition of 5 and 20 μg/mL nivolumab (p = 0.004 and p = 0.004, respectively). Similarly, in the $CD8^+$ T cell group, an increase was observed at all nivolumab concentrations, with the increase being statistically significant at a nivolumab concentration of 10 μg/mL culture (p = 0.032) (Fig. 2A).

T helper or T cytotoxic lymphocytes expressed $CD69^+$

The percentage of Th cells increased at all concentrations of nivolumab, with the increase being statistically significant at nivolumab concentrations of 10 μg/mL culture (p = 0.033) and 20 μg/mL culture (p = 0.016) and at a concentration of 20 μg/mL of culture compared to the lowest concentration of nivolumab used (p = 0.049). In the group of $CD8^+$ T cells, a significant increase was observed at each concentration of nivolumab (5, 10, 20 μg/mL culture) compared to the control culture (p = 0.017; p = 0.006, p = 0.004) (Fig. 2B).

T helper or T cytotoxic lymphocytes expressed $CD95^+$

The percentage of Th cells was higher at all concentrations of nivolumab, with a significant result obtained at the concentrations of 10 and 20 μg/mL (p = 0.01, p = 0.004, respectively). In the T cytotoxic (Tc) cell population, there was a significant increase after stimulation with 10 μg nivolumab (p = 0.016), with a significant decrease in the percentage stimulated with 20 μg nivolumab *vs.* the lowest concentration used (p = 0.033) (Fig. 2C).

T helper or T cytotoxic lymphocytes expressed PD-1 and monocytes expressed PD-L1

In the group of Th lymphocytes, a statistically significant increase in the percentage of cells was observed at each concentration of nivolumab (5, 10, and 20 μg/mL) compared to the unstimulated culture (p = 0.007; p = 0.004; p = 0.01). For cytotoxic T cells, the percentage of cells expressing the PD-1 molecule increased at all concentrations of nivolumab, with the increase being statistically significant at 10 μg/mL (p = 0.003) compared to the control culture and compared to the lowest concentration used (p = 0.008) and at 20 μg/mL (p = 0.006) (Fig. 2D).

Evaluation of the percentage of helper and cytotoxic T lymphocytes and monocytes isolated from peripheral blood stimulated with anti-PD-L1 antibody compared to unstimulated culture

T helper or T cytotoxic lymphocytes expressed $CD25^+$

In the group of Th cells, the percentage of cells significantly increased after the use of atezolizumab at a concentration of 150 μg/mL (p = 0.008), 300 μg/mL (p = 0.013), and 600 μg/mL (p = 0.016) (Fig. 3A).

T helper or T cytotoxic lymphocytes expressed $CD69^+$

In the group of Th cells, a significant increase was observed in the concentration 150 μg/mL — p = 0.009, 300 μg/mL — p = 0.026, and 600 μg/mL — p = 0.008, and among the lymphocyte population Tc (respectively: 150 μg/mL — p = 0.003, 300 μg/mL — p = 0.041, 600 μg/mL — p = 0.003) (Fig. 3B).

T helper or T cytotoxic lymphocytes expressed $CD95^+$

For Th lymphocytes, a significant increase was observed at all concentrations of atezolizumab (150 μg — p = 0.041; 300 μg — p = 0.021; 600 μg — p = 0.026). The percentage of Tc lymphocytes increased significantly at all concentrations of atezolizumab: 150, 300, and 600 μg/mL (respectively: p = 0.013, p = 0.010, p = 0.003) (Fig. 3C).

T helper or T cytotoxic lymphocytes expressed PD-1 and monocytes expressed PD-L1

In the group of $CD4^+$ T lymphocytes, a significant increase was observed at each of the concentrations of atezolizumab compared to the control culture (150 μg — p = 0.021; 300 μg — p = 0.004; 600 μg — p = 0.026). For the Tc cells, a significant increase in the percentage of PD-1-positive cells was observed in each of the concentrations of atezolizumab used (respectively: 150 μg — p = 0.004, 300 μg — p = 0.006, and 600 μg — p = 0.006) compared to the control culture (Fig. 3D). In the group of monocytes, comparing the percentage of analyzed cells in the cultures stimulated with 150 μg and 300 μg atezolizumab, a significant (p = 0.041) decrease in the percentage of analyzed cells was observed at the concentration of 600 μg/mL (Fig. 3E).

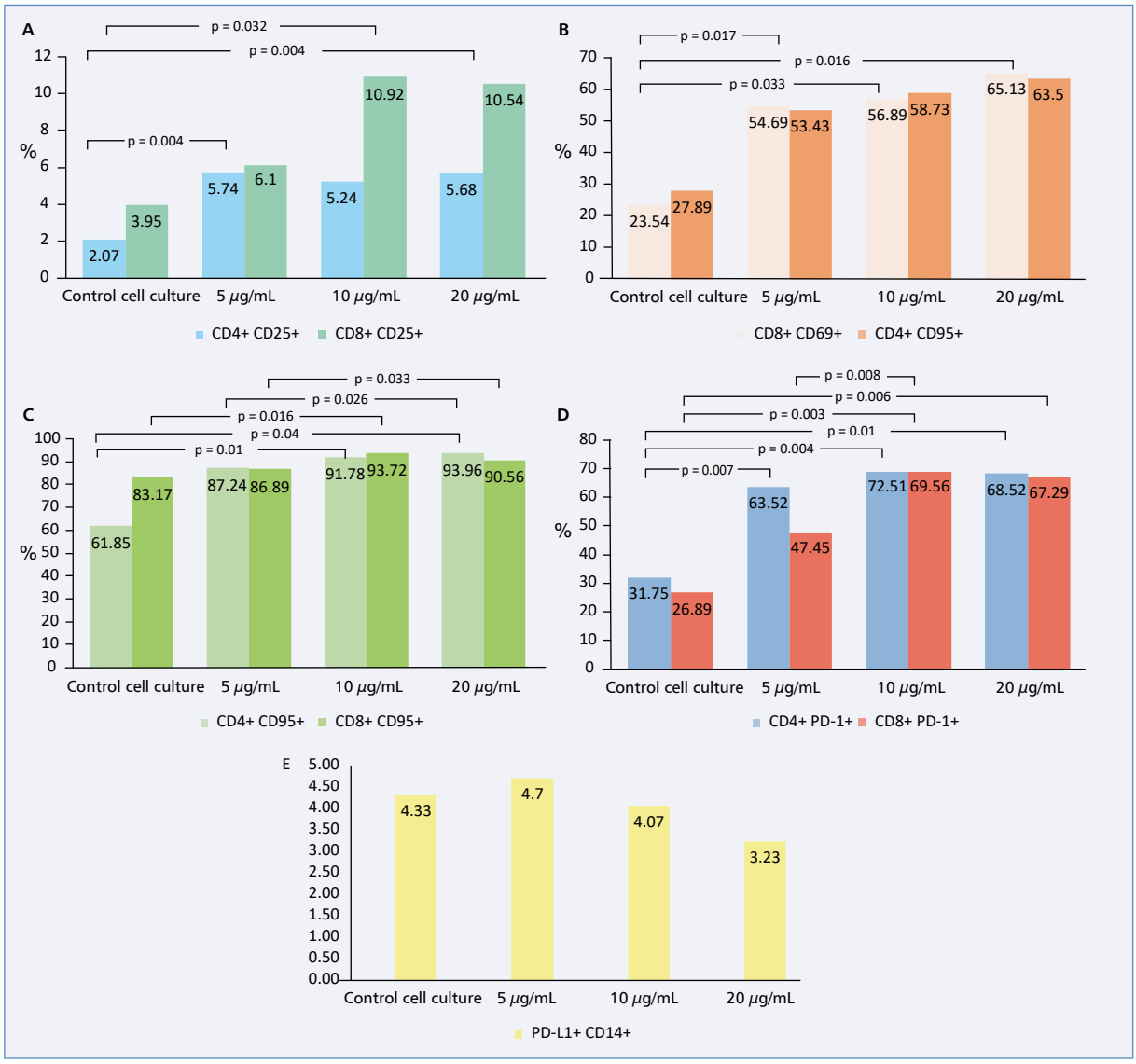

Figure 2. A. Percentage of CD4+ and CD8+ T lymphocytes expressing CD25; **B.** CD69; **C.** CD95; **D.** PD-1; **E.** Percentage of CD14+ monocytes expressing the PD-L1 molecule in the studied cell populations in the material isolated from blood stimulated with various concentrations of nivolumab

Evaluation of expression of the PD-1 molecule on T helper or T cytotoxic lymphocytes isolated from blood and bronchoaspirate stimulated with anti-PD-1 and anti-PD-L1 antibodies compared to unstimulated culture

T helper or T cytotoxic lymphocytes isolated from peripheral blood stimulated with nivolumab

Expression of the PD-1 molecule on the surface of the Th cells significantly decreased in 5 and 10 μg/mL concentrations of nivolumab (respectively $p = 0.01$ and $p = 0.013$), and expression of the PD-1 molecule on the surface of the Tc cells significantly decreased at all concentrations used (5 μg/mL, 10 μg/mL, 20 μg/mL) (respectively $p = 0.005$; $p = 0.003$; $p = 0.004$) (Fig. 4A).

T helper or T cytotoxic lymphocytes isolated from bronchoaspirate stimulated with nivolumab

Expression of the PD-1 molecule on the surface of the Th cells after stimulations of 5 μg/mL and 10 μg/mL nivolumab non-significantly decreased (Fig. 4B).

T helper or T cytotoxic lymphocytes isolated from peripheral blood stimulated with atezolizumab

We also observed that expression of the PD-1 molecule on Th cells decreased in each concentration of atezolizumab. The decrease was significant for 300 μg/mL ($p = 0.003$) and 600 μg/mL ($p = 0.004$) concentrations. PD-1 expression on $CD8^+$T cells decreased

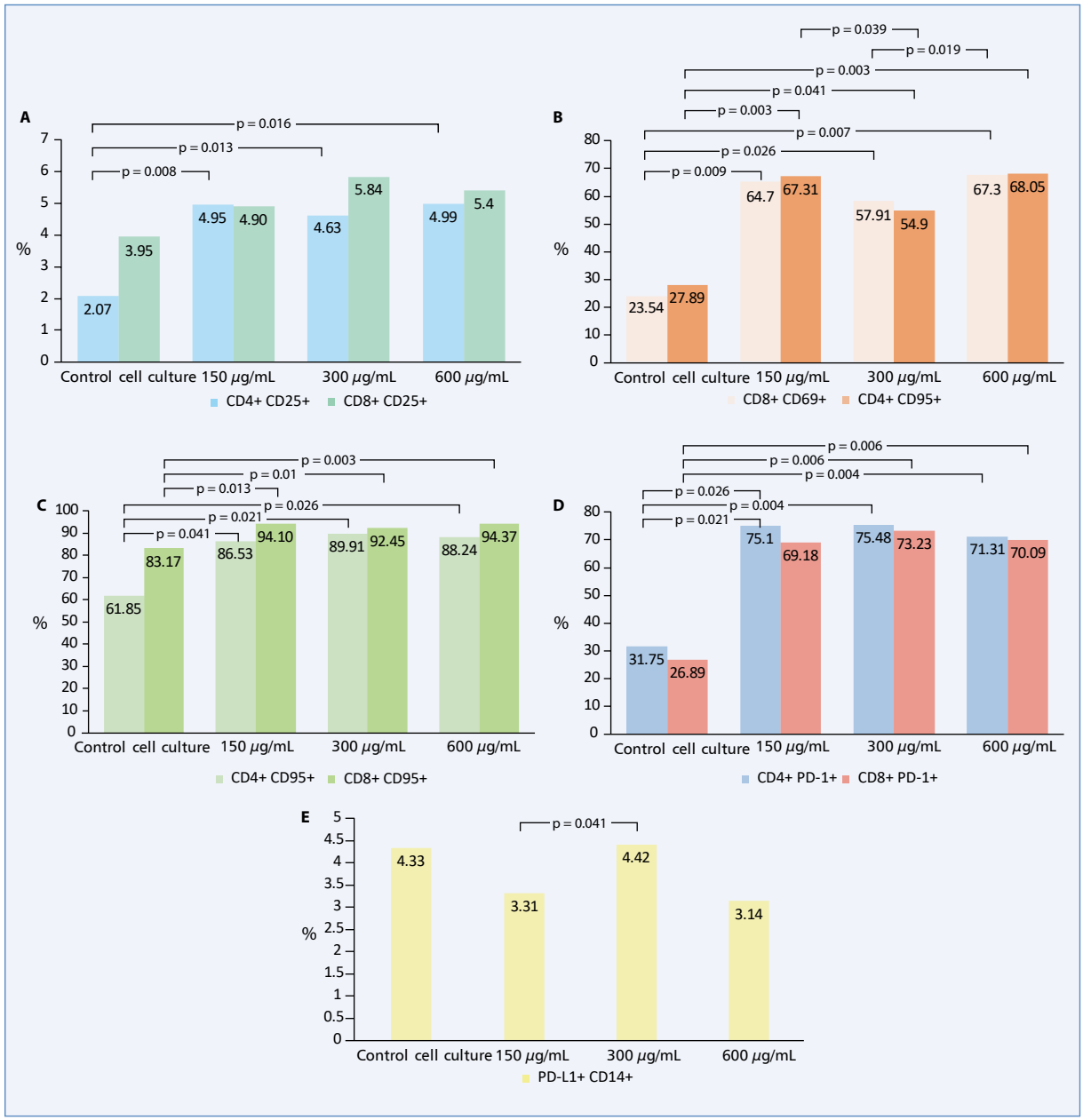

Figure 3. A. Percentage of CD4+ and CD8+ T lymphocytes expressing CD25; **B.** CD69; **C.** CD95; **D.** PD-1; **E.** Percentage of CD14+ monocytes expressing the PD-L1 molecule, in the studied cell populations in the material isolated from peripheral blood stimulated with various concentrations of atezolizumab

after atezolizumab stimulation in each concentration (respectively $p = 0.003$, $p = 0.013$, $p = 0.003$) (Fig. 4C).

T helper or T cytotoxic lymphocytes isolated from bronchoaspirate stimulated with atezolizumab

Expression of the PD-1 molecule on Th lymphocytes was significantly higher in the cell culture stimulated 600 μg/mL of atezolizumab in comparison to the cell culture stimulated by atezolizumab in 300 μg/mL concentrations ($p = 0.041$) (Fig. 4D).

Tables listing all percentages of analyzed cells isolated from peripheral blood and bronchoaspirate (with standard deviations) stimulated with nivolumab or atezolizumab are in Supplementary Tables S1 and S2.

The results on the culture of cells isolated from bronchoaspirate are included in Supplementary material.

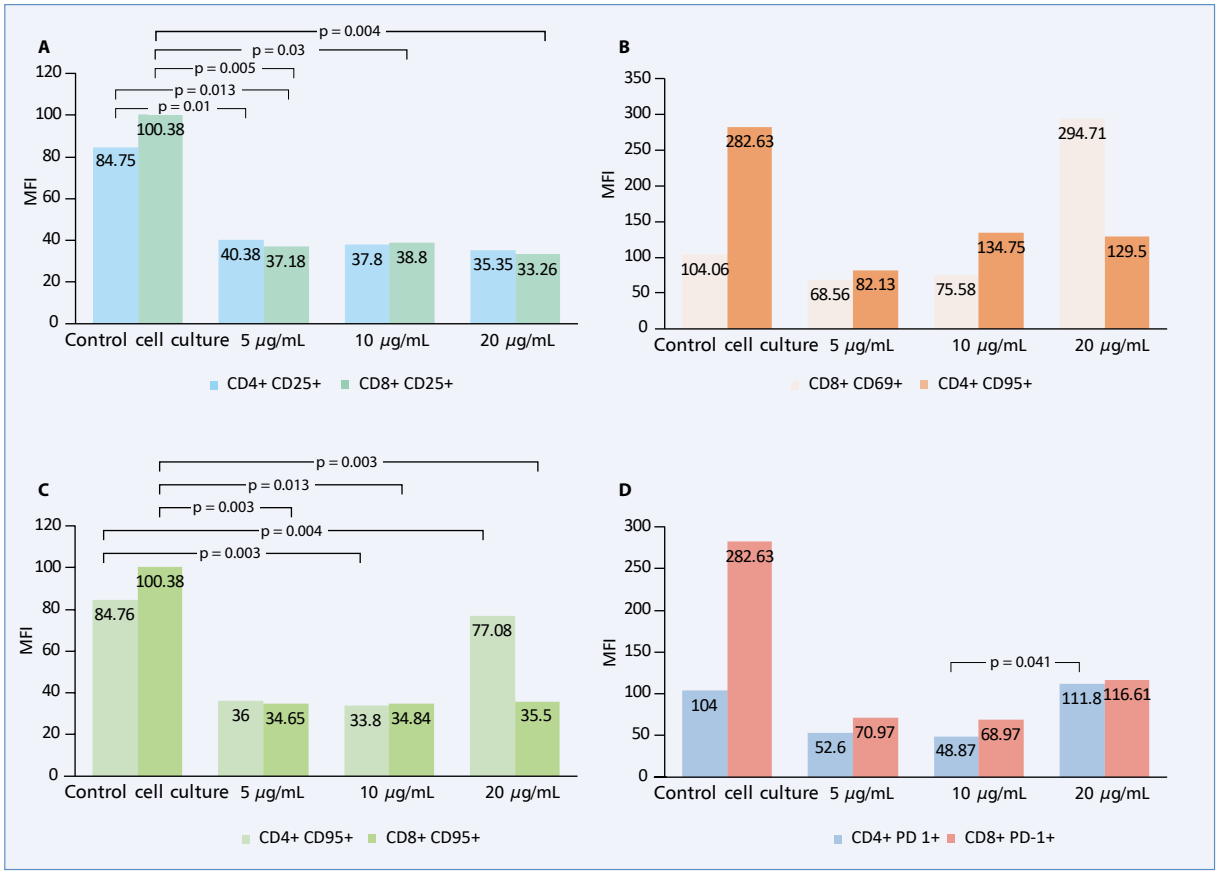

Figure 4. Mean PD-1 fluorescence intensity on the tested populations of CD4+ and CD8+ T cells isolated from blood and bronchoaspirate stimulated by nivolumab (**A, B**) and atezolizumab (**C, D**); MFI — mean fluorescence intensity

Discussion

In this study, we attempted to analyze *in vitro* changes in the immunophenotype and T lymphocyte activity after the use of anti-PD-1 and anti-PD-L1 antibodies. The study showed that checkpoint inhibitors (nivolumab and atezolizumab) have an impact on the blockade of the PD-1/PD-L1 connection. They also influence many functions of immune cells as shown by variable expression of markers analyzed in the study on the surface of T lymphocytes or monocytes, which indicate the current state of the immune system.

The CD25 molecule forms a receptor for interleukin 2 and appears on activated T cells (but does not occur on naive T cells) [4]. In this study, helper and cytotoxic T lymphocytes expressing the CD25 molecule were analyzed and an almost 10-fold higher percentage of $CD4^+/CD25^+$ and $CD8^+/CD25^+$ T cells was observed in the bronchoaspirate than in peripheral blood, which may indicate increased inflammation and increased cell activation in the bronchoaspirate around the tumor. In addition, immunohistochemical analysis confirmed that the presence of activated T lymphocytes has a beneficial effect on the prognosis of NSCLC patients [5].

The CD69 molecule is widely known as an early marker of leukocyte activation, and its main function is to stimulate the proliferation of T lymphocytes in various tissues. Despite this, it turned out that it is also involved in inhibiting the activation of T lymphocytes in the tumor microenvironment [6]. In the presented study, after using different concentrations of nivolumab or atezolizumab, the percentage of CD4-positive and CD8-positive cells expressing the CD69 molecule increased in the cultures of cells isolated from peripheral blood, while expression of this molecule significantly decreased with the increase in the concentration of anti-PD-1 or anti-PD-L1 antibodies compared to the control culture. Such relationships were not observed in cultures of cells isolated from bronchoaspirate. This may indicate a slight response of these cells to stimulation with anti-PD-1 or anti-PD-L1 antibodies and confirm the results of the cited studies on the inhibition of T lymphocyte activation in the tumor microenvironment.

The CD95 molecule (Fas receptor) on the surface of T lymphocytes is primarily a marker of apoptosis of

the cell that will undergo this process after binding to the FasL ligand [7]. The results of our study indicate that with the increase in the concentration of nivolumab, with which the cells isolated from bronchoaspirate were stimulated, the percentage of helper and cytotoxic T cells expressing the CD95 molecule decreased, and the expression intensity of this molecule decreased. In the case of stimulation of the studied cell population with atezolizumab, at the initial concentration (150 μl/mL), the percentage of analyzed T lymphocytes decreased, then increased with increasing concentration, to reach a value comparable to the initial value in the control culture at the highest concentration (600 μl/mL). This may indicate the inhibition of apoptosis of helper and cytotoxic T lymphocytes in the tumor microenvironment after the use of atezolizumab, which may significantly increase the infiltration of tumor tissue by active cells of the immune system. On the other hand, in the cultures of cells isolated from peripheral blood, the opposite situation was observed. When the percentage of tested lymphocytes increased after both nivolumab and atezolizumab, expression of the CD95 molecule decreased. This situation may indicate the influence of anti-PD-1 or anti-PD-L1 antibodies on the stimulation of early apoptosis of circulating helper and cytotoxic T lymphocytes.

Studies conducted over the last few years indicate that cytotoxic T lymphocytes are mainly responsible for direct destruction of cancer cells. Many cells present in the tumor microenvironment cooperate directly or indirectly with CD8-positive T lymphocytes as pro- or anti-cancer cells (including dendritic cells, natural killer cells, and tumor-associated macrophages). For CD8-positive T cells to begin their cytotoxic function, dendritic cells must present them with a tumor antigen in the context of major histocompatibility complex (MHC) class I molecules. During this time, helper T cells secrete cytokines that directly support the differentiation and activation of cytotoxic T cells. In addition, another indirect mechanism of CD8+ T lymphocyte support is the secretion by NK cells and T helper cells of chemokines affecting the maturation and chemotaxis of other innate response cells, including macrophages and dendritic cells [8, 9].

Overexpression of the PD-1 molecule on cytotoxic T lymphocytes and its stimulation by specific ligands contributes to T-cell receptor (TCR) dysfunction and, consequently, to blocking the activity of these cells. Immunotherapy with the use of anti-PD-1 antibodies inhibits the extinction of the activity of these cells, leading to the re-activation of their functions. However, recent studies have shown that reactivated T cells are more likely to be from a group of freshly tumor-infiltrating cells, as they are less regenerative than originally thought [10].

Jin et al. [11] correlated the presence of tumor-infiltrating T cells with expression of PD-L1 on the surface of tumor cells and observed that a high percentage of (tumor-infiltrating lymphocyte (TILs) also had high expression of PD-L1 on tumor cells. The authors conclude that the induction of high PD-L1 expression is certainly one of the mechanisms of defense of cancer cells against the activity of the immune system. At the same time, it is also a predictive marker of the response of such patients to immunotherapy [11].

Gros et al. [12] observed that CD8-positive T cells expressing TCR specific for melanoma antigens were present in the CD8+/PD-1+ lymphocyte fraction, but not in the fraction of cells without the PD-1 molecule. This may suggest that these cells are ready to recognize cancer antigens, and only require unlocking their cytotoxic activity [12, 13].

The tumor microenvironment has a huge and undeniable impact on the activity of the cells of the immune system. The division of tumor types according to the presence of the immune system cells is well described in the literature. The hot type is characterized by strong infiltration of cancer cells by the inactive immune system; the cold type does not have components of the immune system in the tumor tissue; and in the infiltrating type, the immune system marginally penetrates the tumor tissue, but the strong immunosuppressive microenvironment does not allow it to do so [14, 15]. Moreover, it should be borne in mind that effective anti-tumor defense requires the cooperation of both the specific response cells and active non-specific response cells. In our study, no significant effect of the applied antibodies on the activity of monocytes isolated from bronchoaspirate was observed. This may indicate that a single-point approach to immunotherapy — aimed only at stimulating T lymphocyte activity — may not be sufficient to achieve a clinical effect. A comprehensive approach to immunotherapy, in which the activity of T lymphocytes is reactivated and at the same time the activity of non-specific response cells is stimulated, seems to be an interesting approach in the modern treatment of cancer.

Conclusions

In conclusion, our comprehensive analysis of changes in the percentages of T lymphocytes and monocytes examined allows us to draw four significant conclusions:

1. Both anti-PD-1 and anti-PD-L1 antibody stimulation had a more significant effect on the activation of the specific response of PBMCs compared to cells in bronchoaspirate, which may be due to their functional extinction in bronchoaspirate. This material may be a model of the influence of the neoplastic environment on the immune system in the lungs.
2. CD25-positive and CD69-positive helper and cytotoxic T cells are present in the bronchoaspirate of NSCLC patients, but these cells seem unable to form an immune synapse due to the low expression of the CD28 molecule.
3. A decrease in expression of the PD-1 molecule on the surface of the cells of the specific response was observed on mononuclear cells of peripheral blood and bronchoaspirate after stimulation with both anti-PD-1 and anti-PD-L1 antibodies, regardless of the concentration of antibodies used. This indicates the possibility of restoring T lymphocyte function with the use of a minimal dose of anti-PD-1 or anti-PD-L1 antibodies.

Article Information and Declarations

Data availability statement

Original contributions presented in the study are included in the article and further inquiries can be directed to the corresponding author.

Ethics statement

The project received a positive opinion from the Bioethics Committee at the Medical University of Lublin (nr KE-0254/318/2018).

Author contributions

A.B.: conception and design, execution and interpretation of the data being published, wrote the paper; K.W.-K.: conception and design, execution and interpretation of the data being published, supervision; M.N.: supervision; P.K.: execution and interpretation of the data being published.

Funding

Project hasn't additional funding received.

Acknowledgments

None.

Conflict of interest

Authors declare no conflict of interests.

Supplementary material

Tables S1, S2 and results on the culture of cells isolated from bronchoaspirate.

References

4. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol. 2012; 24(2): 207–212, doi: 10.1016/j.coi.2011.12.009, indexed in Pubmed: 22236695.
5. Wojas-Krawczyk K. Podstawy immunoonkologii, cz. 1. Conference „Nowości w leczeniu nowotworów klatki piersiowej", Warszawa 2016.
6. Alonso-García M, Sánchez-Gastaldo A, Muñoz-Fuentes MA, et al. Real-World Analysis of Nivolumab and Atezolizumab Efficacy in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer. Pharmaceuticals (Basel). 2022; 15(5), doi: 10.3390/ph15050533, indexed in Pubmed: 35631359.
7. Gołąb J, Jakóbisiak M, Lasek W, Stokłosa T. Immunologia. PWN 2017.
8. Kayser G, Schulte-Uentrop L, Sienel W, et al. Stromal CD4/CD25 positive T-cells are a strong and independent prognostic factor in non-small cell lung cancer patients, especially with adenocarcinomas. Lung Cancer. 2012; 76(3): 445–451, doi: 10.1016/j.lungcan.2012.01.004, indexed in Pubmed: 22300751.
9. Mita Y, Kimura M, Hayashizaki K, et al. Crucial role of CD69 in anti-tumor immunity through regulating the exhaustion of tumor-infiltrating T cells. International Immunology. 2018; 30(12): 559–567, doi: 10.1093/intimm/dxy050.
10. Risso V, Lafont E, Gallo MLe. Therapeutic approaches targeting CD95L/CD95 signaling in cancer and autoimmune diseases. Cell Death & Disease. 2022; 13(3), doi: 10.1038/s41419-022-04688-x.
11. Wang Q, Xie B, Liu S, et al. What Happens to the Immune Microenvironment After PD-1 Inhibitor Therapy? Front Immunol. 2021; 12: 773168, doi: 10.3389/fimmu.2021.773168, indexed in Pubmed: 35003090.
12. Topalian SL, Taube JM, Anders RA, et al. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer. 2016; 16(5): 275–287, doi: 10.1038/nrc.2016.36, indexed in Pubmed: 27079802.
13. Yost KE, Satpathy AT, Wells DK, et al. Clonal replacement of tumor-specific T cells following PD-1 blockade. Nat Med. 2019; 25(8): 1251–1259, doi: 10.1038/s41591-019-0522-3, indexed in Pubmed: 31359002.
14. Jin Y, Shen X, Pan Y, et al. Correlation between PD-L1 expression and clinicopathological characteristics of non-small cell lung cancer: A real-world study of a large Chinese cohort. J Thorac Dis. 2019; 11(11): 4591–4601, doi: 10.21037/jtd.2019.10.80, indexed in Pubmed: 31903248.
15. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Nat Med. 2016; 22(4): 433–438, doi: 10.1038/nm.4051, indexed in Pubmed: 26901407.
16. Kim KH, Kim CG, Shin EC. Peripheral blood immune cell-based biomarkers in anti-PD-1/PD-L1 therapy. Immune Netw. 2020; 20(1): e8, doi: 10.4110/in.2020.20.e8, indexed in Pubmed: 32158596.
17. Duan Q, Zhang H, Zheng J, et al. Turning Cold into Hot: Firing up the Tumor Microenvironment. Trends Cancer. 2020; 6(7): 605–618, doi: 10.1016/j.trecan.2020.02.022, indexed in Pubmed: 32610070.
18. Bonaventura P, Shekarian T, Alcazer V, et al. Cold Tumors: A Therapeutic Challenge for Immunotherapy. Front Immunol. 2019; 10: 168, doi: 10.3389/fimmu.2019.00168, indexed in Pubmed: 30800125.

Table S1. Cells isolated from blood stimulating by different concetrations of antibodies anti-PD-1 or anti-PD-L1

		Nivolumab			Atezolizumab		
Percentage of cells [%]	Control cell culture	5 μg/mL	10 μg/mL	20 μg/mL	150 μg/mL	300 μg/mL	600 μg/mL
$CD4^+$ $CD25^+$	2.07 ± 2.22	5.74* ± 5.57	5.24 ± 5.47*	5.68** ± 5.18	4.95** ± 3.93	4.63* ± 4.44	4.99* ± 5.09
$CD8^+$ $CD25^+$	3.95 ± 7.04	6.1 ± 6.07	10.92* ± 15.91	10.54 ± 17.05	4.9 ± 7.62	5.84 ± 10.02	5.4 ± 5.08
$CD4^+$ $CD69^+$	23.54 ± 27.70	54.69 ± 26.52	56.89* ± 21.19	65.13* ± 23.52	64.7** ± 18.43	57.91* ± 21.59	67.3** ± 17.99
$CD8^+$ $CD69^+$	27.89 ± 18.40	53.43* ± 24.60	58.73** ± 23.47	63.5** ± 18.32	67.31** ± 14.16	54.9* ± 23.62	68.05** ± 16.64
$CD4^+$ $CD95^+$	61.85 ± 29.08	87.24 ± 13.76	91.78** ± 6.80	93.96* ± 5.24	86.53* ± 17.87	89.91* ± 15.83	88.24* ± 15.59
$CD8^+$ $CD95^+$	83.17 ± 7.67	86.89 ± 17.33	93.72* ± 5.04	90.56 ± 15.01	94.1* ± 5.75	92.45** ± 6.96	94.37** ± 6.22
$CD4^+$ CTLA-4^+ $FoxP3^+$	88.37 ± 8.20	92.23 ± 5.92	90.47 ± 17.74	86.16 ± 19.88	93.26 ± 7.33	87.87 ± 16.65	89.82 ± 3.42
$CD14^+$ B7-$H4^+$	15.14 ± 10.71	9.08 ± 6.02	7.7* ± 4.24	7.8 ± 4.54	6.27* ± 4.66	5.45* ± 3.12	8.67 ± 7.65
$CD14^+$ B7-$H4^+$ IL-10^+	96.73 ± 2.41	97.16 ± 2.04	94.07 ± 11.57	94.5 ± 11.21	94.84 ± 9.68	91.06 ± 18.56	98.02 ± 1.60
$CD4^+$ PD-1^+	31.75 ± 25.04	63.52** ± 24.54	72.51** ± 20.80	68.52* ± 23.89	75.1* ± 17.5	75.48* ± 11.56	71.31* ± 19.86
$CD8^+$ PD-1^+	26.89 ± 18.31	47.45 ± 26.46	69.56** ± 16.98	67.29* ± 21.21	69.18* ± 14.59	73.23* ± 14.02	70.09** ± 13.15
PD-$L1^+$ $CD14^+$	4.33 ± 4.24	4.7 ± 2.48	4.07 ± 2.72	3.23 ± 2.33	3.31 ± 1.86	4.42 ± 2.95	3.14 ± 2.19

*p < 0.05; **p < 0.01

Table S2. Cells isolated from bronchoaspirate stimulating by different concetrations of antibodies anti PD-1 or anti-PD-L1

		Nivolumab			Atezolizumab		
Percentage of cells [%]	Control cell culture	5 μg/mL	10 μg/mL	20 μg/mL	150 μg/mL	300 μg/mL	600 μg/mL
$CD4^+$ $CD25^+$	35.54 ± 27.33	25.64 ± 24.87	25.26 ± 26.12	27.71 ± 21.99	30.25 21.23	36.82 25.62	24.85 22.88
$CD8^+$ $CD25^+$	46.13 ± 27.73	34.05 ± 24.02	38.54 ± 27.20	39 ± 23.32	36.01 ± 29.98	48.19 ± 23.34	42.52 ± 27.95
$CD4^+$ $CD69^+$	48.06 ± 30.01	56.52 ± 29.05	43.21 ± 20.97	55.23 ± 21.57	52.36 ± 24.98	57.51 ± 27.54	58.58 ± 23.46
$CD8^+$ $CD69^+$	54.52 ± 24.44	62.37 ± 21.57	52.45 ± 26.18	61.95 ± 24.85	57.13 ± 27.92	68.23 ± 22.74	71.72 ± 24.15
$CD4^+$ $CD95^+$	72.14 ± 27.87	65.13 ± 29.42	57.54 ± 37.48	58.92 ± 33.28	63.44 ± 26.60	65.52 ± 29.03	73.14 ± 20.67
$CD8^+$ $CD95^+$	81.71 ± 22.14	70.4 ± 19.69	67.4 ± 31.87	64.81 ± 34.71	70.5 ± 33.52	70.72 ± 30.36	81.03 ± 26.74
$CD4^+$ CTLA-4^+ $FoxP3^+$	92.78 ± 1.61	92.28 ± 5.73	93.35 ± 5.47	92.48 ± 5.92	94.9 ± 4.61	93.99 ± 6.25	94.12 ± 6.99
$CD14^+$ B7-$H4^+$	46.03 ± 41.76	50.88 ± 34.96	58.52 ± 27.91	58.62 ± 21.12	57.31 ± 32.01	47.25 ± 31.20	52.37 ± 29.99
$CD14^+$ B7-$H4^+$ IL-10^+	99.17 ± 0.68	99.08 ± 1.36	98.43 ± 2.64	99.27 ± 0.93	99.33 ± 0.99	99.34 ± 1.13	99.33 ± 1.03
$CD4^+$ $PD1^+$	70.87 ± 24.96	57.62 ± 34.82	60.69 ± 31.12	42.26* ± 30.31	62 ± 33.46	68.21 ± 27.91	68.69 ± 27.53
$CD8^+$ PD-1^+	72.23 ± 23.65	62.85 ± 28.12	68.77 ± 27.79	55.62* ± 23.46	63.43 ± 35.66	70.28 ± 31.16	79.59 ± 16.43
PD-$L1^+$ $CD14^+$	40.55 ± 37.01	35.13 ± 35.74	28.4 ± 31.51	27.13 ± 30.62	22.83 ± 25.46	36.55 ± 30.33	28.81 ± 30.66

*p < 0.05; **p < 0.01

Results on the culture of cells isolated from bronchoaspirate

Evaluation of the percentage of helper and cytotoxic T lymphocytes and monocytes isolated from bronchoaspirate stimulated with the anti-PD-1 antibody

T helper or T cytotoxic lymphocytes expressed CD25+, CD69+, or CD95+

In the population of Th lymphocytes, a non-significant decrease in the percentage of cells expressing the CD25 molecule was observed at each of the used anti-PD-1 concentrations compared to the unstimulated culture. In the Tc cell group, the percentage of cells expressing the CD25 molecule was non-significantly lower at all used nivolumab concentrations than in the control culture (Fig. S1A). In the Th lymphocyte population, a non-significant increase in the percentage of CD69-positive cells was observed at the lowest concentration of nivolumab (5 μg/mL) compared to the control culture. Then, at the concentration of 10 μg/mL, the percentage decreased insignificantly, and after the application of 20 μg nivolumab in culture, the percentage of $CD4^+/CD69^+$ cells increased insignificantly compared to the unstimulated culture. In the Tc cell group, the percentage of CD69-positive cells increased non-significantly at the lowest nivolumab concentration of

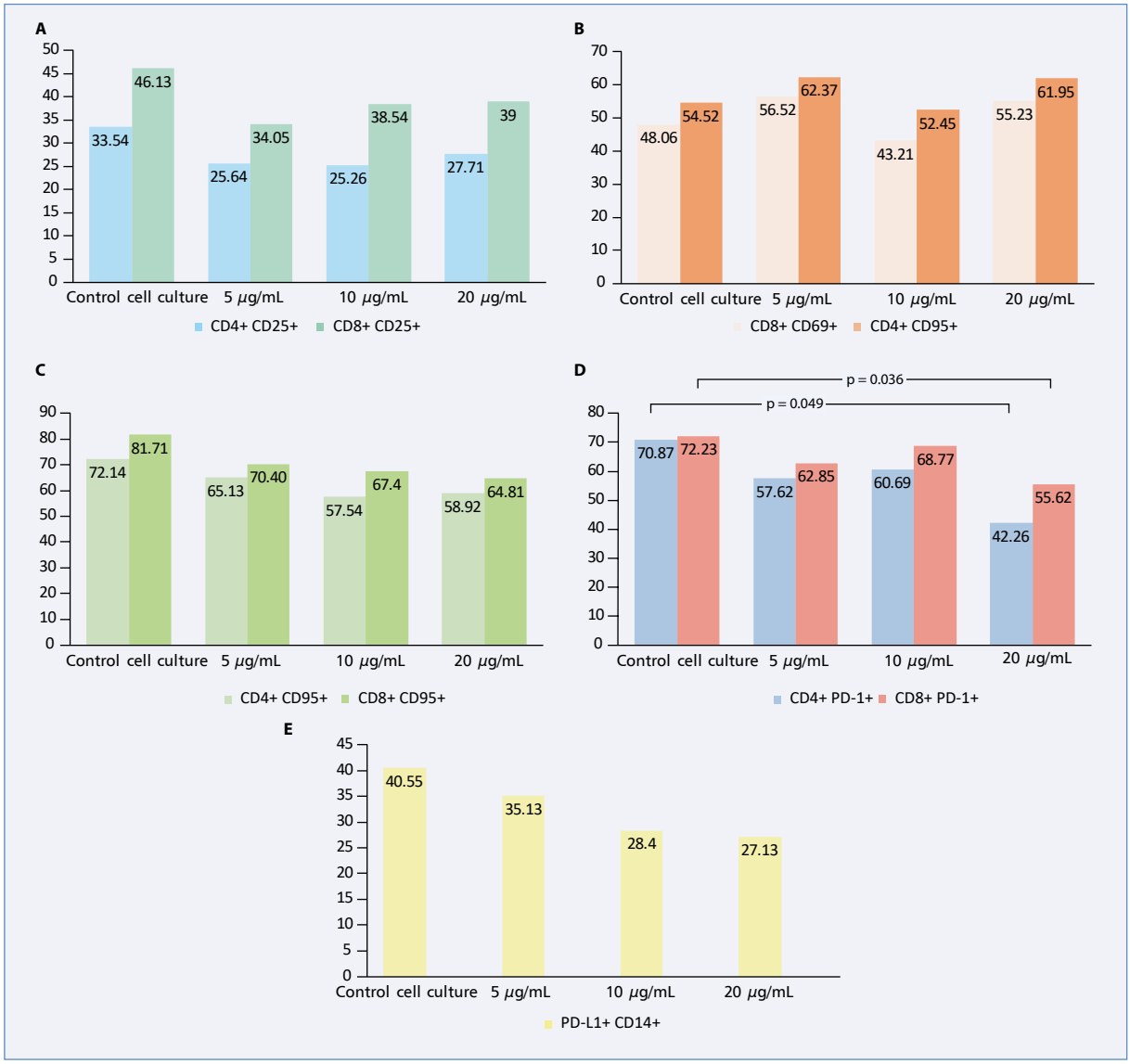

Figure S1. A. Percentage of CD4+ and CD8+ T lymphocytes expressing CD25; **B.** CD69; **C.** CD95; **D.** PD-1; **E.** Percentage of CD14+ monocytes expressing the PD-L1 molecule on the molecules on the studied cell populations in the material isolated from bronchoaspirate stimulated with various concentrations of nivolumab

5 μg/mL relative to the control culture, then decreased at the next concentration (10 μg/mL) compared to the control culture, and increased again non-significantly at the highest (20 μg/mL) concentration of nivolumab relative to the control culture (Fig. S1B). In the group of Th lymphocytes, a decrease in the percentage of cells expressing the CD95 molecule was observed at all concentrations of nivolumab compared to the control culture. Similarly, in the group of $CD8^+$ T cells, a non-significant decrease in the percentage of cells expressing the CD95 molecule was observed, with increasing nivolumab concentration compared to the unstimulated culture (Fig. S1C).

T helper or T cytotoxic lymphocytes expressed PD-1 and monocytes expressed PD-L1

Among the helper T cells, a decrease in the percentage of cells expressing the PD-1 molecule was observed at all concentrations of nivolumab compared to the control culture, and it was statistically significant at the nivolumab concentration of 20 μg/mL ($p = 0.049$) compared to the control culture. In the group of Tc cells, the percentage of cells expressing the PD-1 molecule was lower compared to the control culture, but significantly lower at the nivolumab concentration of 20 μg/mL ($p = 0.036$) (Fig. S1D). At each of the used concentrations of nivolumab, the percentage of monocytes expressing the PD-L1 molecule was non-significantly lower compared to the control culture, with this value being the lowest at the highest concentration used (Fig. S1E).

Evaluation of the percentage of helper and cytotoxic T lymphocytes and monocytes isolated from bronchoaspirate stimulated with anti-PD-L1 antibody

T helper or T cytotoxic lymphocytes expressed CD25+, CD69+ or CD95+

In the helper T cell group, a statistically significant decrease in the percentage of $CD4^+/CD25^+$ cells ($p = 0.016$) compared to 300 μg/mL was observed in the cultures stimulated with atezolizumab at a concentration of 600 μg/mL. At the other concentrations of atezolizumab (150 μl and 300 μg/mL), a non-significant decrease and an increase in the percentage of cells expressing the CD25 molecule were observed, respectively, compared to the control culture. In the group of $CD8^+$ T cells, only cultures stimulated with the anti-PD-L1 antibody at a concentration of 300 μg/mL showed a non-significant increase in the percentage of $CD8^+/CD25^+$ cells compared to the control culture. In the remaining concentrations of this antibody, the percentage of analyzed cells was insignificantly lower than in the control cultures (Fig. S2A). Both helper (CD4-positive) and cytotoxic (CD8-positive) T cell groups showed a non-significant increase in the percentage of cells expressing the CD69 molecule at all atezolizumab concentrations compared to the control culture (Fig. S2B). The percentage of CD95-positive Th cells was non-significantly higher compared to the control culture only in cultures stimulated with the anti-PD-L1 antibody at a concentration of 600 μg/mL. At the remaining concentrations of the anti-PD-L1 antibody, the percentage of these cells was non-significantly lower than in the control culture. The percentage of CD95-positive Tc cells was non-significantly lower at each used concentration of atezolizumab compared to the control culture (Fig. S2C).

T helper or T cytotoxic lymphocytes lymphocytes expressed PD-1 and monocytes expressed PD-L1

In the helper T cell population, the percentage of cells expressing the PD-1 surface molecule was non-significantly lower at all atezolizumab concentrations compared to the control culture. In the group of cytotoxic T cells, a non-significant decrease in the percentage of cells expressing the PD-1 molecule was observed (Fig. S2D). In the monocyte group, a non-significant decrease in the percentage of cells expressing the PD-L1 molecule was observed (Fig. S2E).

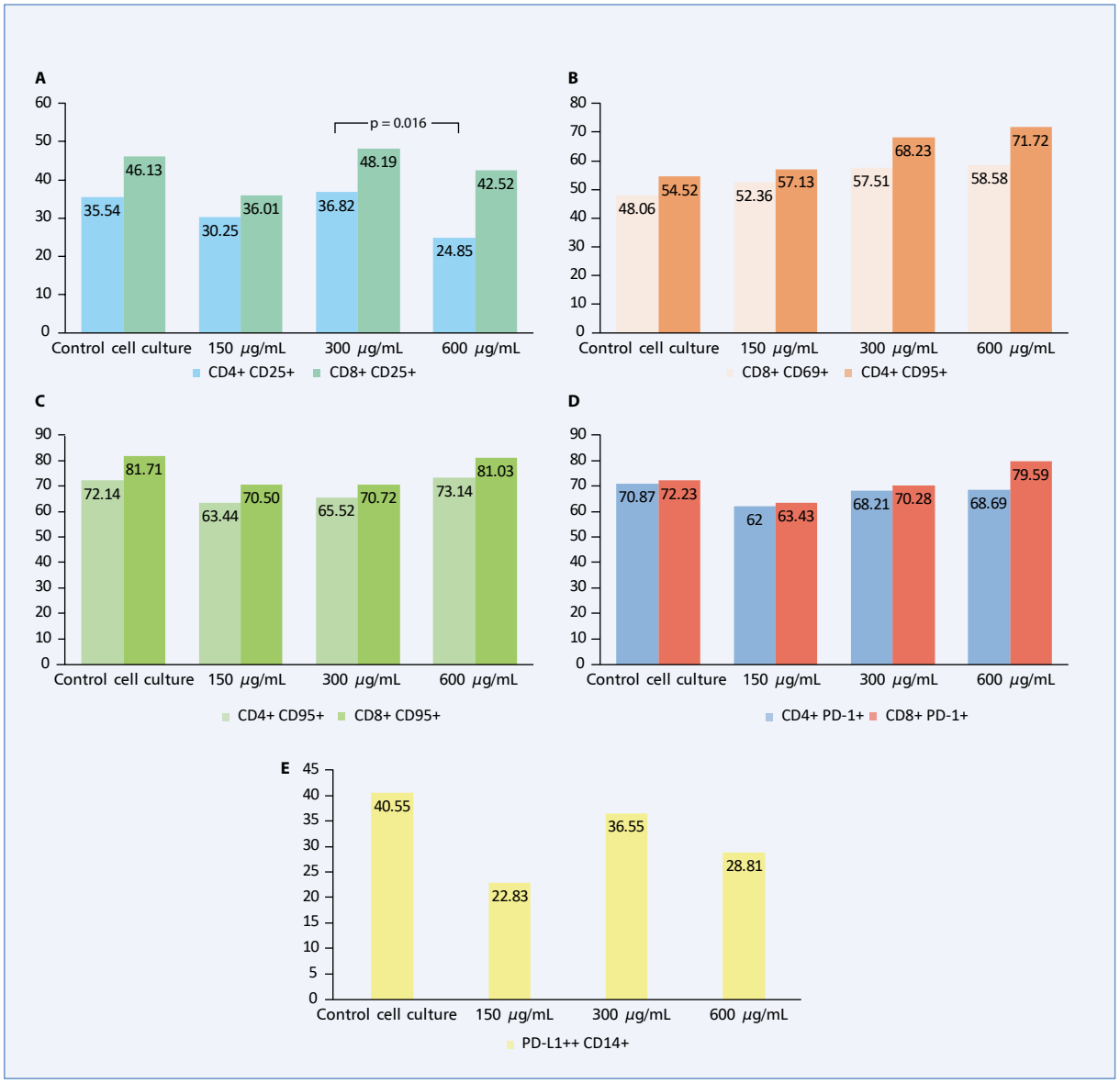

Figure S2. A. Percentage of CD4+ and CD8+ T lymphocytes expressing CD25; **B.** CD69; **C.** CD95; **D.** PD-1; **E.** Percentage of CD14+ monocytes expressing the PD-L1 molecule on the molecules on the studied cell populations in the material isolated from bronchoaspirate stimulated with various concentrations of atezolizumab

VIA MEDICA

CASE REPORT

Adam Fałkowski[1], Aleksandra Żołnierek[2], Jakub Żołnierek[1]

[1]LUX MED Onkologia, Warsaw, Poland
[2]Faculty of Medicine, Medical University of Warsaw, Poland

Spectacular clinical benefit achieved by multidisciplinary management of a kidney cancer patient

Address for correspondence:
Jakub Żołnierek, MD, PhD
LUX MED Onkologia
ul. Szamocka 6, 01–748 Warsaw, Poland
e-mail: qbazolnier@wp.pl

Oncology in Clinical Practice
DOI: 10.5603/OCP.2023.0037

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

The present study is a case report of a patient with a diagnosis of renal cell carcinoma with poor prospects, in whom long-term tumor control at the level of deep cytoreduction was achieved through aggressive multidisciplinary management using surgery, stereotactic radiotherapy, and sequential systemic therapy with immunotherapy based on a checkpoint inhibitor with anti-PDL1 activity combined with anti-angiogenic treatment, and by a non-selective tyrosine kinase inhibitor.

Keywords: renal cell carcinoma, multidisciplinary treatment, molecularly targeted drugs, immune checkpoint inhibitors

Oncol Clin Pract 2024; 20, 2: 136–143

Introduction

According to the Polish National Cancer Registry's report, 2727 men and 1755 women developed kidney cancer in 2020. The disease caused the deaths of 1434 men and 946 women. Among solid tumors, kidney cancer is the seventh (for men) and ninth (for women) most commonly diagnosed histological type of cancer in Poland [1].

Case report

In August 2012, a right kidney tumor was diagnosed in, at that time, a 52-year-old active and fit man. The lesion was initially visualized by abdominal ultrasonography (USG), which was performed in the course of the diagnosis of recurrent and worsening right lumbar pain observed for several preceding weeks and followed by an episode of macroscopic hematuria. The location of the pole-positioned tumor and dimensions of 67 × 66 × 76 millimeters were confirmed by a computed tomography (CT) scan while ruling out the presence of other lesions.

The patient had type 2 diabetes mellitus (which was well controlled with insulin use from 2001) and persistent hypothyroidism (which was secondary to a thyroidectomy performed in November 2012 due to cystic goiter, compensated with levothyroxine supplementation).

The patient received a radical right-sided nephrectomy (on 17 September 2012). On pathomorphological examination, we diagnosed a clear-cell renal cell carcinoma with a rhabdoid component (ccRCC) with a high Furhman grade (G4) at the pT1bNx stage. In the post-surgery period, the patient remained under clinical observation and received periodical radiological check-ups.

After approximately two years, that is, in November 2014, a follow-up CT scan showed a recurrence of the cancer in the form of dissemination to the liver (Fig. 1). In addition to the largest lesion of 45 mm in diameter, which had been observed earlier and recognized as

Received: 01.06.2023 Accepted: 01.06.2023 Early publication date: 30.06.2023

a hemangioma, three further metastatic tumors of up to 15 mm in diameter appeared in the organ. Furthermore, a dynamic growth of a mediastinal lymph node located paratracheally with ambiguous dimensions of 13 × 18 mm was observed during CT. No abnormalities were visualized in the post-nephrectomy bed.

An exploratory laparoscopy procedure was performed with conversion to laparotomy, and two sections of metastatic tumor were taken. Clear cell cancer type in the tissue specimen was confirmed.

Due to the spread of the neoplastic process with the metastatic location described above, a decision was made to qualify the patient for systemic treatment. Given the availability of an experimental treatment using next-generation immunotherapy and anti-angiogenic treatment in February 2015, the patient was enrolled in the phase II clinical trial NCT01984242 (after obtaining his informed consent). In this study, causative treatment included atezolizumab (ATEZO), an immune checkpoint inhibitor with anti-PD-L1 activity, and bevacizumab (BEV), a monoclonal antibody with anti-angiogenic activity.

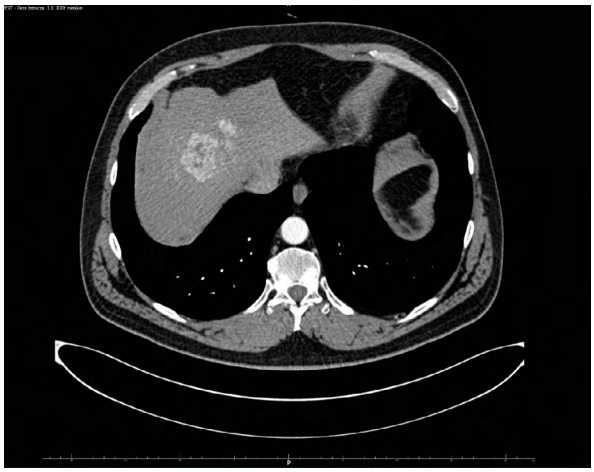

Figure 1. Recurrence in the form of dissemination to the liver (2014)

The patient received and tolerated this treatment, apart from moderate secondary hypertension, which was well controlled with a beta-blocker. Clinically significant adverse effects were virtually non-existent.

The systemic treatment went smoothly, but a follow-up CT scan (performed in August 2015) showed a new hypervascular lesion with metastatic morphology and a dimension of 19 × 13 millimeters, in the choroid plexus of the left lateral ventricle of the brain (Fig. 2).

This was observed in addition to stabilization of the measurable liver lesions. Tumor progression with a new lesion was confirmed by magnetic resonance imaging (MRI) of the central nervous system with the use of a contrast agent.

The patient did not consent to the proposed neurosurgical treatment involving removing the lesion in his brain, but he decided to try radiosurgery, and only if radiosurgery was confirmed as unsuccessful, he agreed to consider surgical treatment. In September 2015, the patient underwent stereotactic radiosurgery (SRS), with the use of a Gamma Knife. Radiation was applied at a dose of 18 Gy in one fraction to a target of 5.8 cm^3.

Given his good tolerance of the local treatment, the absence of general or focal neurological deficits or clinical and radiographic features of tumor progression in the central nervous system, at withdrawal of anti-edematous treatment with corticosteroids, the patient was put back to immunotherapy with the approval of the trial sponsor. At the same time, the decision was made to withhold anti-angiogenic treatment due to safety concerns.

Subsequent imaging assessments using CT imaging revealed complete remission (CR) of the metastatic liver lesions — scarred hypodense areas remained at the site of the hypervascular foci, which did not undergo contrast

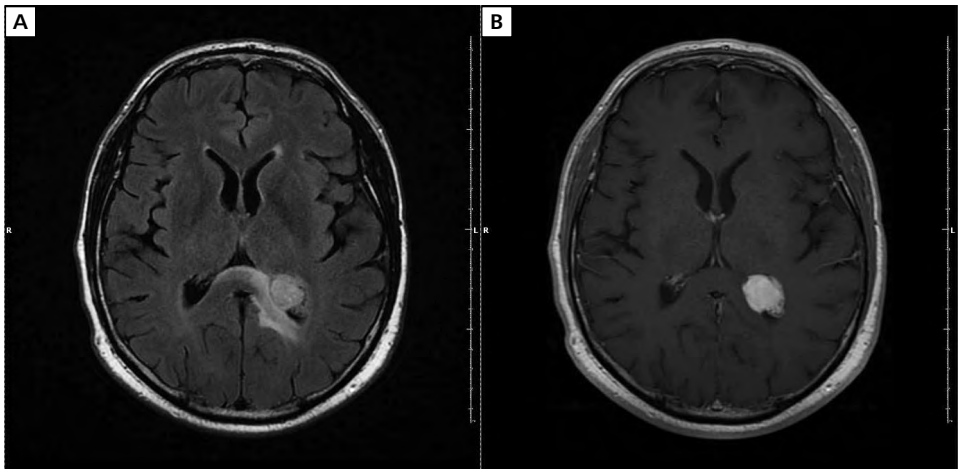

Figure 2A–B. New metastatic lesion in the choroid plexus of the left lateral ventricle (2015)

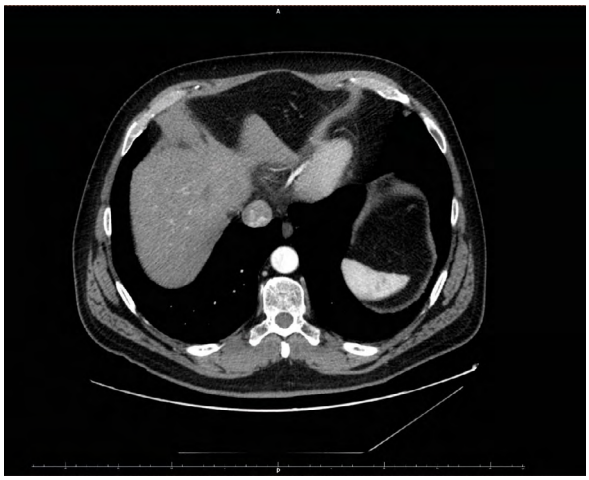

Figure 3. Complete remission of metastatic lesions in the liver (2017)

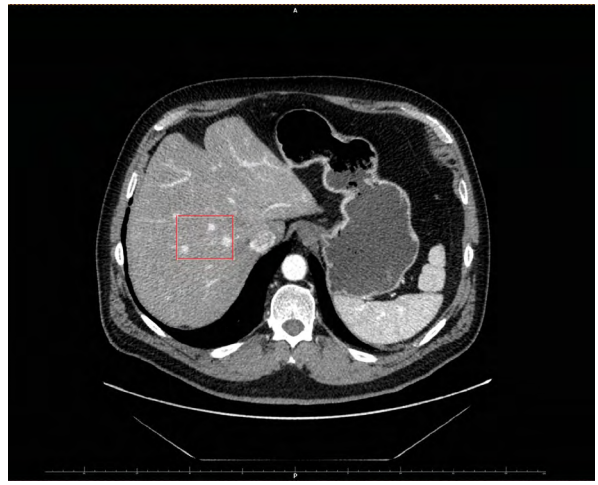

Figure 4. Progression of the disease in the liver, with the metastatic lesions highlighted in the frame (2019)

enhancement (Fig. 3). Regular MR imaging confirmed radiation necrosis of the metastasis after SRS use.

In August 2017, the treatment with atezolizumab was discontinued, due to another tumor progression in the form of a solitary metastatic lesion enlargement to a size of 15 × 20 mm in a lymph node located in the aortopulmonary window. For this reason, the patient was again qualified for SRS at a dose of 30 Gy administered in three fractions.

In the course of regular follow-up examinations after this treatment phase, including positron emission tomography (PET), no features of malignancy were found. In particular, MRI of the brain described further regression of the hypervascular lesion in the vicinity of the left lateral ventricular triangle.

During this period, the patient remained under observation. He felt well. He did not display any symptoms suggestive of cancer recurrence.

However, in January 2019, a routine follow-up CT scan of the patient, who still had no symptoms, revealed progression with the appearance of focal lesions in both lungs (dimensions up to 10 mm), nodal lesions in the mediastinum and lung hilum (up to 20 mm in the short dimension), and in the pancreas (up to a maximum diameter of 22 × 17 mm). The recurrence of the renal cell carcinoma was dynamic, as a follow-up CT performed a few weeks later showed the appearance of approximately ten hypervascular focal lesions up to 14 mm in size in the liver (Fig. 4).

A decision was made to use cabozantinib, an oral multikinase inhibitor with anti-angiogenic activity, exerted through inhibitory effects on vascular endothelial growth factor receptor (VEGFR)-related kinases. The drug also stimulates antiproliferative activity, through inhibition of MET and AXL kinases. Treatment with a tyrosine-kinase inhibitor (TKI), which had become available only a few months earlier, began in April 2019, under the accelerated access program. The drug was administered at a typical daily dose of 60 mg once per day.

As several adverse effects were associated with the treatment, a change to the cabozantinib dosing regimen was required.

After a transient and clinically insignificant increase in hepatic transaminase activity, which normalized after the temporary introduction of hepatoprotective drugs (e.g. ornithine aspartate), diarrhea became the main problem. An adverse event of grade 2 intensity according to the CTCAE (Common Terminology Criteria for Adverse Events) occurred despite the patient's adherence to the recommended dietary restrictions and was alleviated to grade 1 intensity after interventional use of loperamide in several daily doses and its prophylactic use (1–2 tablets before the first meal each day). The patient reported gastrointestinal disorders, which were present already before treatment under the extended access program for cabozantinib, and a family history in this respect, which warranted further diagnosis by performing a colonoscopy. During the procedure, no significant abnormalities were found apart from a small 3-mm polypus, which was removed and verified microscopically as a hyperplastic lesion. Chronic loosening of stools with exacerbations to diarrhea of G1 severity, secondary to dietary errors, resulted in annoying irritation of the anal area, with a sensation of severe burning aggravated after defecation accompanied by periodic itching. Damage to the mucosa and skin around the anus required topical treatment with hydrocortisone ointment.

During the course of TKI treatment, hand-foot skin reaction (HFSR) lesions of grade 3 and a papulopustular rash of grade 1 according to CTCAE also occurred. The skin lesions required two-week discontinuation of the drug and, together with adverse events described above, eventually a reduction of the daily

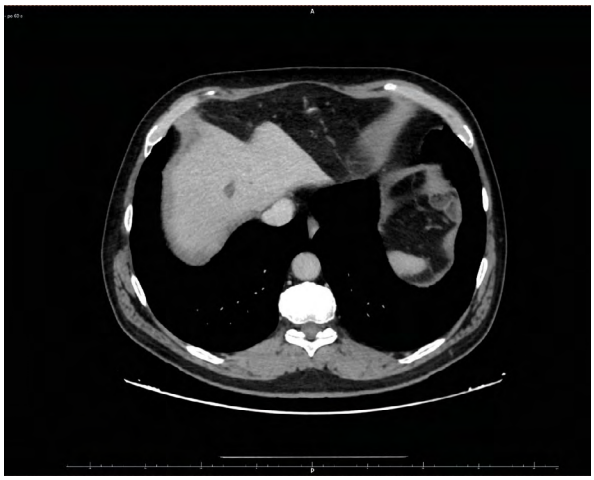

Figure 5. Cicatricial hypodense liver lesions (2023)

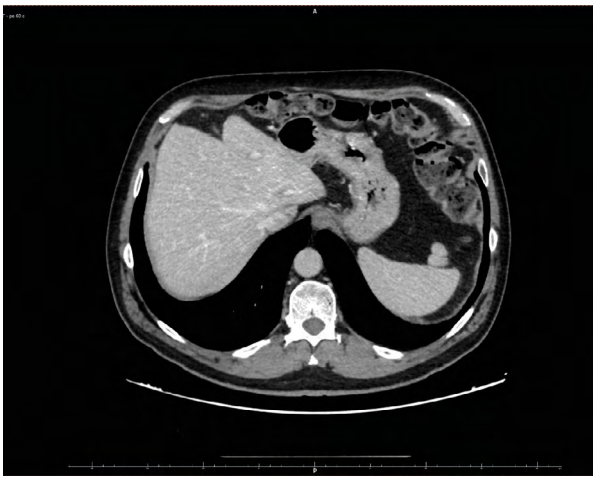

Figure 6. Regression of metastases in the liver (2023)

dose to 40 mg in August 2019, significantly improving treatment tolerability.

Blood pressure was well controlled. However, systolic hypertension persisted in the afternoon, which was the reason for introduction of amlodipine. Given the incomplete response, the patient was referred to cardiology counseling after a Holter examination, and it was decided to use a preparation containing perindopril and amlodipine, which was successful.

In laboratory tests, apart from hyperglycemia and the aforementioned elevation of aminotransferases, no clinically significant abnormalities were observed. Improvement in glycemia occurred after diabetology consultation, correction of insulin doses, and changes in dietary habits.

To date, (June 2023) that is, for a period of four years after the start of cabozantinib treatment, the disease remains under TKI control. In the last imaging assessment performed in March and April 2023, signs of regression of the metastatic tumor in the brain structures (MRI of the brain), and the absence of pathological contrast enhancement within this lesion was confirmed. At the same time, a profound response (very good partial remission, VGPR) of peripheral metastatic lesions (CT) was found (Fig. 5, 6) — we found a complete regression of secondary lesions from the lung parenchyma, scarred hypodense liver lesions, and calcified involutional foci in the pancreatic parenchyma resembling post-inflammatory lesions of 1–2 mm in size (Fig. 7).

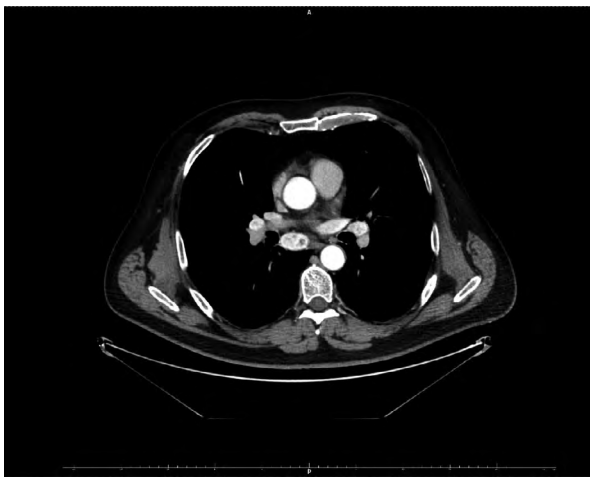

Figure 7. Nodal recurrence in the mediastinum (2019)

Discussion

The course of treatment of renal cell carcinoma in this patient demonstrates the clinical benefits that can be achieved by taking an aggressive approach using all available management modalities, from localized progression to recurrence with dissemination. Nowadays, the standard for planning treatment strategies is to use available methods when patients' general condition and the other analyzed variables allow the use of treatment. A decade ago, experience with multidisciplinary treatment was starting to build. At that time, the role of surgical treatment — typically limited to nephrectomy and palliative orthopedic or neurosurgical procedures — was being discussed. The role of radiotherapy, used mainly as a palliative treatment for metastatic foci in the bones or as whole-brain irradiation for central nervous system metastases, was considered. The effectiveness was evaluated, and the optimal use of systemic treatments with anti-angiogenic drugs was sought. After using TKIs, the objective response rate (ORR) was expected to be achieved in about 30% of patients (usually — partial responses, rarely — complete

responses), and median progression-free survival (PFS) reached about 11 months and median overall survival (OS) about two years. The above parameter values for evaluating the efficacy of TKIs are derived from registration and comparative studies of sunitinib and pazopanib, most commonly used in the first-line systemic treatment of patients with generalized clear cell renal cell carcinoma [2–5]. The typical, at that time, a clinical situation when a significantly locally advanced renal tumor is diagnosed only after onset of alarming symptoms with hematuria is now seen much less frequently. Nowadays, most of the primary lesions in the kidney are found incidentally at an early stage of development, which makes it possible to eliminate the risk of dissemination worsening the prognosis. The procedure performed in patients diagnosed with significantly locally advanced renal cell carcinoma used to involve complete removal of the kidney. Currently, when the location of the tumor within the kidney allows, a sparing procedure is preferred.

Nowadays, when the presentation of local or loco-regional stage and/or higher histological/nuclear grade of the primary tumor is observed with high risk of tumor recurrence (30–50%), adjuvant treatment is considered.

Anti-angiogenic TKIs, despite attempts to use them in this indication, have failed [6–12]. They did not provide a benefit in terms of prolonging disease-free survival (DFS) or significantly improving OS. Sunitinib was one exception. The benefit of adjuvant treatment with sunitinib, compared to observation, was clinically debatable when the risk of TKIs generating side effects and the cost of treatment are taken into account. The weakness of TKIs in adjuvant treatment is probably due to the mechanism of anti-tumor action itself. Neo-angiogenesis begins to play an important role in promoting the growth of tumor lesions only after tumor micro-focuses have reached a critical tumor mass. Antiangiogenic treatment has no effect on small lesions, which are secondarily responsible for recurrence. The effect of preventing recurrence persists for the duration of active TKI use and disappears after treatment is discontinued.

The publication of the results of the KEYNOTE-564 trial, in which pembrolizumab was used as an adjuvant treatment, was a breakthrough in adjuvant treatment [13]. Compared to placebo, adjuvant immunotherapy for patients with tumors at high risk of recurrence/spread [pT2 G4 or pT3 — irrespective of G trait, and/or N(+) — irrespective of T and G trait, or NED (no evidence of disease) tumors after oligo resection] statistically and clinically significantly increased DFS. The benefit was greater in cases of more advanced resected tumors and/or tumors characterized by greater histologic malignancy. The KEYNOTE-564 data on evaluating the impact of the intervention on OS are still immature. Interestingly, analogous trials of adjuvant use of atezolizumab or ipilimumab with nivolumab have failed [14, 15].

In the case we described, the neoplasm was relatively small, but the complex histologic composition with a rhabdoid component determined the rather rapid recurrence of the neoplasm in the form of dissemination.

After the diagnosis of tumor recurrence, data confirming the relatively low activity of available TKIs against tumors with histology other than clear cell (in particular, lesions with either a sarcomatoid or rhabdoid component) were taken into account. Faced with the possibility of an experimental systemic treatment, intensifying classical anti-angiogenic therapy with a drug from the next-generation immunotherapy group, the patient agreed to participate in a clinical trial.

At present, the choice of treatment with an immune checkpoint inhibitor in combination with antiangiogenic treatment seems natural, but that method of disease management is not reimbursed in Poland. However, according to international recommendations [16–18] — it is the treatment of choice, which should be considered first. The treatment regimen used in the patient, combining atezolizumab and bevacizumab, ultimately failed to gain registration — in a conducted clinical trial, there was no advantage over sunitinib. Nevertheless, several other prospective phase III clinical trials demonstrated that treatment with immunotherapy together with TKIs is effective and safe [19–22].

The benefits of two-drug regimens are achieved by taking advantage of the completely different mechanisms of action of their components. The tyrosine kinase inhibitor exerts an almost immediate inhibitory effect on tumor growth. It allows for overcoming the weakness of immunotherapy, which consists in the slow and staggered generation of a clonal immune response directed against tumor cells. This phenomenon is the cause of early progression, which can occur within the first three to six months of immunotherapy in about half of patients. In addition, TKI induces necrosis within tumor lesions and leads to the release or exposure of further tumor antigens (neoantigens), which increases immunogenicity. In contrast, immunotherapy included in two-drug regimens is responsible for generating long-lasting therapeutic responses, which translate into prolonged OS. Following a two-drug regimen, we expect an ORR rate of 50–60% (including about 10% complete remission of lesions), median PFS of 18 months and median OS exceeding 40 months. This spectacular effect is particularly evident in patient populations with unfavorable or very unfavorable prognosis on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) scale and in tumors of complex histology with the presence of a sarcoma component.

The case presented here concerns a patient classified as having a favorable prognosis on the IMDC scale. However, it is obvious that the parameters considered in determining the prognostic category in this scale, do not exhaust all the clinical conditions that have a potential impact on the survival time of patients.

The administered treatment was well tolerated. Experience gained over several years of intensive use of PD-1/PD-L1 inhibitor-based immunotherapy in various cancer diagnoses indicates that it is a safe treatment provided that complications are recognized promptly and appropriate management is followed. Most side effects associated with immunotherapy are moderate in severity and can be easily managed with supportive treatment or deferral of immunotherapy infusion [19–24]. Allergic reactions are rare. Nevertheless, it should be remembered that some patients develop reactions that are severe and life-threatening. Those reactions are mainly induced by an autoimmune mechanism with involvement of the gastrointestinal tract, liver, lungs, or, less frequently, the heart, central or peripheral nervous system structures, and kidneys. Therefore, education of patients and caregivers about early signs of potential toxicity with new-generation immunotherapy is crucial for safe provision of causal treatment. The goal of that education is to sensitize patients to the need to react quickly and contact the medical center when symptoms that may suggest treatment toxicity arise. The identification of specific side effects allows for early differential diagnosis and appropriate symptomatic or causal treatment with glucocorticosteroids or, in extreme cases, immunosuppression.

In our patient, the metastatic lesion in the central nervous system was exposed and grew. At the same time, good control of "peripheral" metastatic lesions was confirmed. The mentioned situation of so-called oligoprogression (increase in the isolated number of metastatic lesions) was due to weaker biological effects induced by immunotherapy. Cells of the immune system (including helper and cytotoxic lymphocytes) penetrate the brain structures to a lesser extent, which allows the growth of metastatic lesions. The fact that a metastatic lesion in the brain is revealed within the first six months after the start of causal systemic treatment suggests its formation even before the initiation of therapy. It was decided to implement local treatment, and the patient made his choice by undergoing stereotactic radiotherapy. The issue of systemic treatment was discussed extensively in correspondence with the sponsor of the clinical trial, with the final decision to continue it. The decision, as further observation of the disease course confirmed, turned out to be the right one.

Eventually, however, after further two years, it became necessary to terminate immunotherapy. The reason was another cancer progression, in the form of an isolated enlargement to 15 × 20 mm of a metastatic altered lymph node in the aortopulmonary window, which was an indication for a repeat local treatment. However, for formal reasons dictated by the provisions of the clinical trial protocol, after the second episode of tumor progression was detected, treatment with atezolizumab was stopped. The tumor progression escaping treatment was irradiated. Since radiographically documented remission of the remaining tumor lesions was achieved, the patient was referred for active observation, which allowed him to function normally for another 18 months. Nevertheless, in January 2019, another recurrence occurred with tumor dissemination appearing as multiple metastatic lesions in both lungs, mediastinal lymph nodes, pancreas, and liver.

In daily clinical practice, oncologists use the imperfect Response Evaluation Criteria in Solid Tumors (RECIST) classification system for causal treatment, which was developed mainly to monitor effects of chemotherapy and is not optimal for evaluating response to treatment with molecularly targeted drugs or immunotherapy. The use of RECIST in cases of slow growth of pre-existing tumor foci may suggest observation of the patient as the best course of action. In the case described here, with dynamic growth of existing lesions and new metastatic foci, there was no doubt about the necessity for prompt initiation of next-line systemic treatment. The decision was fairly obvious, but the choice of second-line therapy was a subject of discussion. At that time, there was no data to make an informed choice of treatment after the failure of previously administered immunotherapy.

The efficacy of sunitinib or pazopanib after failure of antiangiogenic treatment (in our case — bevacizumab) was poorly documented. Both drugs are listed as highly effective when used as first-line systemic therapy. Tivozanib was unavailable, and everolimus — an inhibitor of the mammalian target of rapamycin (mTOR) complex — with a 2% objective response rate and median PFS of four to five months was a purely palliative option. Moreover, due to its toxicity profile, everolimus was not a valuable option for a patient with diabetes as a comorbidity. Axitinib, which is a selective VEGF receptor inhibitor with almost exclusively anti-angiogenic activity, had registration [25]. However, the efficacy of axitinib was documented mainly for the sequential use after treatment with sunitinib (cases of axitinib use after bevacizumab accounted for about 10% of the population evaluated in the registration trial and was not high). The objective response rate in the AXIS trial was estimated at 20%, and median PFS at five months. In addition, later analyses [26] indicated that axitinib should be used in patients with small tumor masses, as significant process progression and localization of metastases in the liver significantly limits the activity of this TKI.

Cabozantinib, a recently registered non-selective new-generation TKI with high antineoplastic and antiproliferative activity due to inhibition of AXL and MET kinases, seemed to be the optimal choice. Both of these proteins have a significant impact on the biology of renal cell carcinomas [27, 28]. Constitutively stimulated, they are responsible for aggressive tumor growth, invasion, and metastasis formation early in the process. Thus, the use of a drug that inhibits AXL and MET function may be decisive in overcoming secondary resistance and offer a chance for clinical benefit. In the METEOR registration study, cabozantinib, compared to everolimus after the failure of prior TKI-based treatment, showed a statistically and clinically significant advantage with regard to the ORR, median PFS, and median OS. The rates were 21% *versus* 5% and 7.4 months *versus* 3.8 months, for the ORR and PFS, respectively. A 33% reduction in the relative risk of death was also demonstrated ($p = 0.005$). In addition, cabozantinib was shown to be highly effective for metastases localized in the bone and liver, as well as when tumor progression was significantly advanced. The above circumstances justified the use of cabozantinib in a patient who was relatively young and in good general performance status with dynamically growing cancer with a starting point in the kidney. Cabozantinib was used as part of the extended access programme. The course of treatment has been described above. Apart from the long-lasting and profound TKI response achieved, attention should be paid to treatment tolerability. Typically for a non-selective tyrosine kinase inhibitor, significant toxicities are observed. The described management with the introduction of lifestyle and nutrition modifications, appropriate symptomatic and supportive treatment, modification of cabozantinib dosing regimen preceded by differential diagnosis, indicates the important role of the above-mentioned management methods with the participation of experts from other specialities. The measures taken have translated into success, which, without a doubt, is the patient's survival of more than seven years, counted from the start of treatment of the disseminated renal cell carcinoma.

As mentioned in the introduction of the paper, the presented case report — although describing an increasingly common scenario of multidisciplinary treatment today — is interesting from the perspective of a clinician in Poland. After the introduction of new generation immunotherapy into reimbursement and wider possibilities of sequential treatment within the B.10. drug programme [29]. In the authors' opinion, it may facilitate therapeutic decision-making and support the building of their own experience in the use of molecularly targeted drugs and immune checkpoint inhibitors in patients with generalised renal cell carcinoma.

Article Information and Declarations

Ethics statement

Prepared with patient consent to use anonymised medical data.

Author contributions

A.F., J.Ż.: medical care, collection and analysis of clinical data, preparation of the manuscript.
A.Ż.: clinical data analysis, preparation of the manuscript and translation of the study into English.

Acknowledgments

We would like to thank the patient and his family and other members of the LuxMed Oncology team for their support.

Conflict of interest

A.F.: professional fees for conducting clinical trials from the following companies: Janssen, BMS, MSD, Merck, Pfizer, Ipsen, Roche — with no influence on the design of the study or the content contained therein.
J.Ż.: professional fees for lectures and participation in advisory committees from the following companies: Janssen, MSD, Astra Zeneca, Pfizer. Professional fees for conducting clinical trials from the following companies: Janssen, BMS, MSD, Merck, Pfizer, Ipsen, Roche — no influence on the design of the study or the content contained therein.
A.Ż.: declare no conflict of interest.

References

1. Narodowy Instytut Onkologii. Nowotwory złośliwe w Polsce w 2020 roku. https://onkologia.org.pl/sites/default/files/publications/2023-01/nowotwory_2020.pdf (15.05.2023).
2. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356(2): 115–124, doi: 10.1056/NEJMoa065044, indexed in Pubmed: 17215529.
3. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6): 1061–1068, doi: 10.1200/JCO.2009.23.9764, indexed in Pubmed: 20100962.
4. Escudier B, Porta C, Bono P, et al. Patient preference between pazopanib (Paz) and sunitinib (Sun): Results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma (mRCC)—PISCES study, NCT 01064310. J Clin Oncol. 2012; 30(15_suppl): CRA4502–CRA4502, doi: 10.1200/jco.2012.30.15_suppl.cra4502.
5. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013; 369(8): 722–731, doi: 10.1056/NEJMoa1303989, indexed in Pubmed: 23964934.
6. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016; 387(10032): 2008–2016, doi: 10.1016/S0140-6736(16)00559-6, indexed in Pubmed: 26969090.
7. Ravaud A, Motzer RJ, Pandha HS, et al. S-TRAC Investigators. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med. 2016; 375(23): 2246–2254, doi: 10.1056/NEJMoa1611406, indexed in Pubmed: 27718781.
8. Haas NB, Manola J, Dutcher JP, et al. Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the

ASSURE randomized trial. JAMA Oncol. 2017; 3(9): 1249–1252, doi: 10.1001/jamaoncol.2017.0076, indexed in Pubmed: 28278333.
9. Motzer RJ, Haas NB, Donskov F, et al. PROTECT investigators. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017; 35(35): 3916–3923, doi: 10.1200/JCO.2017.73.5324, indexed in Pubmed: 28902533.
10. Motzer RJ, Russo P, Haas N, et al. PROTECT study investigators. Adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma: final overall survival analysis of the phase 3 PROTECT trial. Eur Urol. 2021; 79(3): 334–338, doi: 10.1016/j.eururo.2020.12.029, indexed in Pubmed: 33461782.
11. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann Oncol. 2018; 29(12): 2371–2378, doi: 10.1093/annonc/mdy454, indexed in Pubmed: 30346481.
12. Oza B, Eisen T, Frangou E, et al. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: results from the SORCE randomized phase III intergroup trial. J Clin Oncol. 2020; 38(34): 4064–4075, doi: 10.1200/JCO.20.01800, indexed in Pubmed: 33052759.
13. Choueiri TK, Tomczak P, Park SeH, et al. KEYNOTE-564 Investigators. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med. 2021; 385(8): 683–694, doi: 10.1056/NEJMoa2106391, indexed in Pubmed: 34407342.
14. Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2022; 400(10358): 1103–1116, doi: 10.1016/S0140-6736(22)01658-0, indexed in Pubmed: 36099926.
15. Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. Lancet. 2023; 401(10379): 821–832, doi: 10.1016/S0140-6736(22)02574-0, indexed in Pubmed: 36774933.
16. ESMO. Renal Cell Carcinoma: ESMO Clinical Practice Guidelines. https://www.esmo.org/guidelines/guidelines-by-topic/genitourinary-cancers/renal-cell-carcinoma. (15.05.2023).
17. EAU Guidelines on Renal Cell Carcinoma. https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Renal-Cell-Carcinoma-2023.pdf (15.05.2023).
18. NCCN. Kidney Cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf (15.05.2023).
19. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020; 21(12): 1563–1573, doi: 10.1016/S1470-2045(20)30436-8, indexed in Pubmed: 33284113.
20. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019; 380(12): 1103–1115, doi: 10.1056/NEJMoa1816047, indexed in Pubmed: 30779531.
21. Choueiri TK, Powles T, Burotto M, et al. CheckMate 9ER Investigators. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021; 384(9): 829–841, doi: 10.1056/NEJMoa2026982, indexed in Pubmed: 33657295.
22. Motzer R, Alekseev B, Rha SY, et al. CLEAR Trial Investigators. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med. 2021; 384(14): 1289–1300, doi: 10.1056/NEJMoa2035716, indexed in Pubmed: 33616314.
23. Motzer RJ, Escudier B, George S, et al. Nivolumab versus everolimus in patients with advanced renal cell carcinoma: Updated results with long-term follow-up of the randomized, open-label, phase 3 CheckMate 025 trial. Cancer. 2020; 126(18): 4156–4167, doi: 10.1002/cncr.33033, indexed in Pubmed: 32673417.
24. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020; 5(6): e001079, doi: 10.1136/esmoopen-2020-001079, indexed in Pubmed: 33246931.
25. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011; 378(9807): 1931–1939, doi: 10.1016/S0140-6736(11)61613-9, indexed in Pubmed: 22056247.
26. Bracarda S. Abstract 589. ASCO GU 2018 Congress.
27. Chung BI, Malkowicz SB, Nguyen TB, et al. Expression of the proto-oncogene Axl in renal cell carcinoma. DNA Cell Biol. 2003; 22(8): 533–540, doi: 10.1089/10445490360708946, indexed in Pubmed: 14565870.
28. Zhou L, Liu XD, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2016; 35(21): 2687–2697, doi: 10.1038/onc.2015.343, indexed in Pubmed: 26364599.
29. Obwieszczenie Ministra Zdrowia z dnia 20 lutego 2023 r. w sprawie wykazu leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 marca 2023 r. https://www.gov.pl/web/zdrowie/obwieszczenie-ministra-zdrowia-z-dnia-20-lutego-2023-r-w-sprawie-wykazu-lekow-srodkow-spozywczych-specjalnego-przeznaczenia-zywieniowego-na-1-marca-2023-r (15.05.2023).

VIA MEDICA

CASE REPORT

Yassir Benameur[1, 2], Salah Nabih Oueriagli[1], Omar Ait Sahel[1], Abderrahim Doudouh[1, 3]

[1]Department of Nuclear Medicine, Mohammed V Military Teaching Hospital, Rabat, Morocco
[2]Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco
[3]Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco

Cardiac metastasis of lung cancer diagnosed by fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)

Address for correspondence:
Yassir Benameur, MD
Department of Nuclear Medicine,
Mohammed V Military Teaching Hospital
10045, Rabat, Morocco
e-mail: benameur.yassir@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/ocp.95808

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Lung cancer is currently one of the most common malignancies worldwide. Among all metastatic sites of this cancer, cardiac metastases are exceptional, and long-term prognosis in these patients is very poor. ^{18}F-FDG PET/CT is a valuable imaging tool for initial staging and assessment of treatment response of various neoplasms. In the case of lung cancer, its role is clearly defined, and its effectiveness is superior to other diagnostic imaging methods. We present a rare ^{18}F-FDG PET/CT image finding in a 71-year-old man with biopsy-proven lung squamous cell carcinoma, showing increased cardiac ^{18}F-FDG uptake subsequently found to be compatible cardiac metastasis.
Keywords: cardiac metastasis, FDG, lung cancer, PET/CT

Oncol Clin Pract 2024; 20, 2: 144–147

Introduction

The most common metastatic sites in lung cancer are the nervous system, bones, liver, respiratory system, and adrenal glands [1]. Cardiac metastasis from lung cancer is rare and usually difficult to diagnose unless it causes symptoms. Most often it is discovered during assessment by fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT).

We describe a case of squamous cell lung carcinoma with metastasis to the right ventricle detected by FDG-PET/CT.

Case report

A 71-year-old man, a former smoker affected by arterial hypertension, presented with a cough, left chest pain, exertional breathlessness, and a weight loss of 10 kg in 4 months. Physical examination revealed reduced chest movements on the left anterior side of the chest and decreased intensity of breath sounds on auscultation. Computed tomography (CT) of the chest showed a large heterogeneous enhancing mass lesion measuring 6.7 cm × 7.2 cm × 7.4 cm with a spiculated margin in the lower lobe of the left lung.

Received: 30.05.2023 Accepted: 18.08.2023 Early publication date: 17.10.2023

Computed tomography-guided biopsy confirmed the diagnosis of poorly differentiated squamous cell carcinoma. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography was performed to investigate potential metastases and, in addition to a hypermetabolic lung mass in the lower lobe (SUV_{max} = 14.3), it showed (1) lesions with increased FDG uptake in the left hilar and mediastinal lymph nodes and on the left iliac wing compatible with bone metastasis, (2) an intracardiac FDG-avid mass with SUV_{max} = 11.2 measuring 3.8 cm × 6.1 cm × 3.9 cm, suggesting a right ventricle metastasis.

The patient underwent transthoracic ultrasound and cardiac magnetic resonance imaging (CMR) for further evaluation and tissue characterization of the mass. Cardiac magnetic resonance imaging imaging showed a right ventricular mass, with high-signal intensity on T2-weighted imaging, hypoperfused on first-pass perfusion relative to the myocardium, and with late gadolinium hyperenhancement. These findings were consistent with the tumor diagnosis and likely represented metastatic disease.

Our patient was treated with palliative chemotherapy and died from general deterioration of his condition 6 months after the diagnosis.

Discussion

Heart tumors are rare and difficult-to-diagnose pathologies. Most primary cardiac tumors are benign in origin, and secondary cardiac tumors are more common than primary cardiac malignancies [2]. The incidence is higher than one may expect and ranges from 2.3% to 18.3% [3]. In theory, any cancer can lead to cardiac metastases. The most common cancers are melanoma, lung, breast, esophageal, and hematological malignancies [4]. These metastases are most often located in the right heart [5]. The myocardium is the most frequently metastatically affected cardiac tissue, followed by the pericardium and then the endocardium; conduction system involvement is much less common [6]. Metastasis can reach the heart through the dissemination of cancer cells into the bloodstream, or directly via adjacent tissues; another way is propagation via the superior or inferior vena cava to the right atrium [7]. In the case of lung cancer, metastatic cells often reach the heart through the lymphatic system; they usually do not cause any symptoms and are, therefore, rarely diagnosed before death [8].

The diagnosis of metastatic cardiac tumors is often delayed due to diverse and nonspecific manifestations, especially in early stages. In more advanced stages, secondary tumors of the heart gradually lead to heart failure, conduction disorders, valve diseases, such as mitral stenosis, angina pain, Adams-Stokes syndrome, and even sudden death. Such outcomes have been reported in approximately 3% of patients with cardiac metastases [9]. Electrocardiogram (ECG) changes are non-specific; in most cases, the ECG is normal. However, the following abnormalities may be observed: low voltage, ischemia, heart blocks, and arrhythmias [10]. Imaging studies have turned out to be very useful noninvasive tools for diagnostic evaluation of cardiac metastases. According to the 2022 European Society of Cardiology (ESC) Cardio-Oncology Guidelines, in the case of cardiac metastases, imaging can assess the possibility of heart surgery and may include echocardiography, CMR, computed tomography, and FDG-PET/CT [11]. Transthoracic echocardiography (TTE) or transesophageal echocardiography is the initial imaging test to detect *cardiac metastases.* It evaluates the size, location, mobility, and extent of pericardial invasion of the tumor [12]. Cardiovascular magnetic resonance adds information about tumor size, morphology, location, extent of invasion degree, and vascularity [13]. Fluorodeoxyglucose positron emission tomography/computed tomography provides a combination of data on tumor morphology and metabolism, which is relatively objective. Additionally, FDG-PET/CT features may be useful in distinguishing malignant and nonmalignant cardiac lesions, but this remains controversial [14].

Since histopathological confirmation of the cardiac metastases in our patient was not performed, we cannot completely rule out the possibility of other diseases. The differential diagnosis excluded cardiac thrombosis or the presence of a chemotherapy catheter [11] and included other causes of malignant or benign primary cardiac tumors. Most primary cardiac tumors are benign: myxomas, rhabdomyomas, papillary fibroelastoma, fibromas, hemangiomas, lipomas, and leiomyomas [15]. Cardiac sarcoma accounts for more than two-thirds of all primary cardiac malignant tumors, and histopathological subtypes of primary cardiac sarcoma include angiosarcoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, synovial sarcoma, fibrosarcoma muscle and undifferentiated pleural sarcoma [16].

In our patient with aggressive lung cancer, the cardiac mass was considered secondary, and treatment was initiated.

In such cases, total surgical resection remains the treatment of choice, recommended in the 2022 ESC Cardio-Oncology Guidelines, but this option was not feasible due to high postoperative morbidity and the need for adjuvant radiotherapy or chemotherapy.

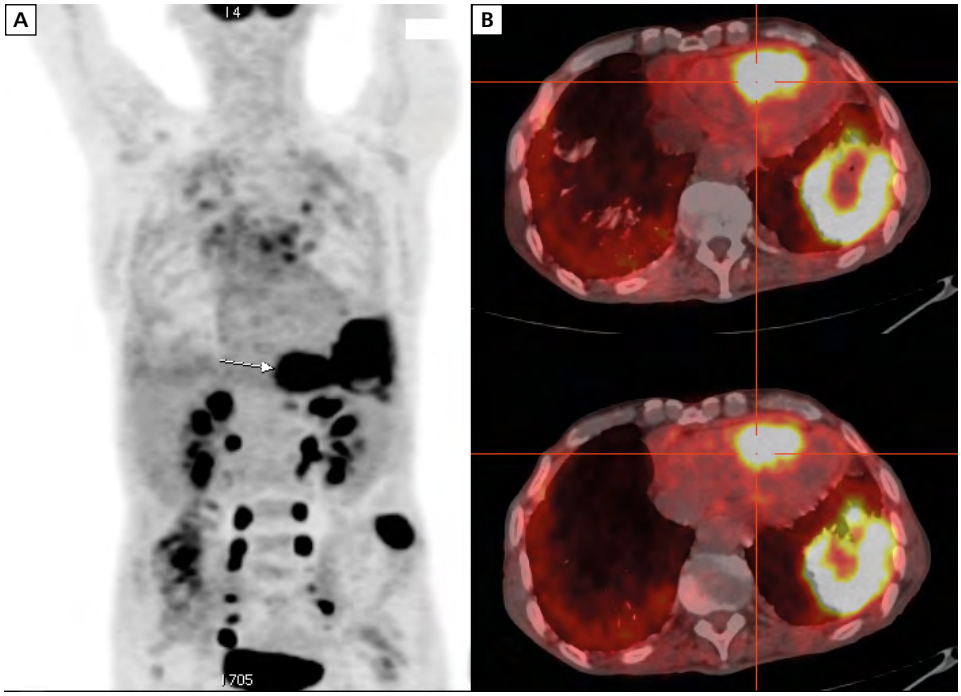

Figure 1. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT): maximum intensity projection maximum intensity projection (MIP) (**A**), and transaxial images of the thorax (**B**), showing an intense and pathological FDG uptake in the right ventricle (white arrow in MIP)

Conventional radiotherapy is mainly used in palliative situations to bring relief to symptomatic patients [17].

The prognosis of patients with malignant cardiac tumors depends on many factors and, despite advances, remains generally *poor*, with *survival ranging* from 6 to 18 months after the diagnosis [18].

Conclusions

Our case demonstrates that FDG-PET/CT is an effective imaging modality for detecting rare distant metastatic sites, which can result in changing disease management. It increases chances of detecting cardiac metastases at an early stage thus facilitating adequate treatment.

Article Information and Declarations

Ethics statement

The patient's consent was obtained for the presentation of a clinical case.

Author contributions

Y.B.: article concept, writing, clinical data collection, literature data collection; S.N.O.: clinical data collection; O.A.S.: clinical data collection; A.D.: supervising and revising the article.

All authors have read and agreed to the published version of the manuscript.

Funding

None.

Acknowledgments

None.

Conflict of interest

Authors declare no conflict of interest.

Supplementary material

None.

References

1. Riihimäki M, Hemminki A, Sundquist K, et al. The epidemiology of metastases in neuroendocrine tumors. Int J Cancer. 2016; 139(12): 2679–2686, doi: 10.1002/ijc.30400, indexed in Pubmed: 27553864.
2. Paraskevaidis IA, Michalakeas CA, Papadopoulos CH, et al. Cardiac tumors. ISRN Oncol. 2011; 2011: 208929, doi: 10.5402/2011/208929, indexed in Pubmed: 22091416.
3. Bussani R, De-Giorgio F, Abbate A, et al. Cardiac metastases. J Clin Pathol. 2007; 60(1): 27–34, doi: 10.1136/jcp.2005.035105, indexed in Pubmed: 17098886.

4. Murad R, Bakkar R, Sukkar R, et al. A Case of Ewing Sarcoma Presenting With Cardiac Metastasis. World J Pediatr Congenit Heart Surg. 2019; 10(5): 632–634, doi: 10.1177/2150135119846047, indexed in Pubmed: 31496409.
5. Reynen K, Köckeritz U, Strasser RH. Metastases to the heart. Ann Oncol. 2004; 15(3): 375–381, doi: 10.1093/annonc/mdh086, indexed in Pubmed: 14998838.
6. Shehata BM, Thomas JE, Doudenko-Rufforny I. Metastatic carcinoid to the conducting system-is it a rare or merely unrecognized manifestation of carcinoid cardiopathy? Arch Pathol Lab Med. 2002; 126(12): 1538–1540, doi: 10.5858/2002-126-1538-MCTTCS, indexed in Pubmed: 12456219.
7. Lahmidi I, Assoweh CD, Haddiya I, et al. Clinicopathological features of adult right-sided cardiac masses: Analysis of 19 cases. Ann Med Surg (Lond). 2022; 77: 103613, doi: 10.1016/j.amsu.2022.103613, indexed in Pubmed: 35638074.
8. Das A, Das SK, Pandit S, et al. Bronchogenic Carcinoma with Cardiac Invasion Simulating Acute Myocardial Infarction. Case Rep Oncol Med. 2016; 2016: 7813509, doi: 10.1155/2016/7813509, indexed in Pubmed: 27042370.
9. Ito T, Ishikawa N, Negishi T, et al. Cardiac metastasis of tongue cancer may cause sudden death. Auris Nasus Larynx. 2008; 35(3): 423–425, doi: 10.1016/j.anl.2007.04.017, indexed in Pubmed: 17855031.
10. Lyon AR, López-Fernández T, Couch LS, et al. ESC Scientific Document Group. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022; 43(41): 4229–4361, doi: 10.1093/eurheartj/ehac244, indexed in Pubmed: 36017568.
11. Burazor I, Aviel-Ronen S, Imazio M, et al. Metastatic cardiac tumors: from clinical presentation through diagnosis to treatment. BMC Cancer. 2018; 18(1): 202, doi: 10.1186/s12885-018-4070-x, indexed in Pubmed: 29463229.
12. Bogren HG, DeMaria AN, Mason DT. Imaging procedures in the detection of cardiac tumors, with emphasis on echocardiography: a review. Cardiovasc Intervent Radiol. 1980; 3(3): 107–125, doi: 10.1007/BF02552329, indexed in Pubmed: 6991115.
13. Yin H, Mao W, Tan H, et al. Role of F-FDG PET/CT imaging in cardiac and pericardial masses. J Nucl Cardiol. 2022; 29(3): 1293–1303, doi: 10.1007/s12350-020-02510-9, indexed in Pubmed: 33462788.
14. Dos Santos VM, Dos Santos LA. Cardiac and lymphatic metastases from lung cancer. Arch Iran Med. 2018; 21(2): 82–83, indexed in Pubmed: 29664660.
15. Tyebally S, Chen D, Bhattacharyya S, et al. Cardiac Tumors: State-of-the-Art Review. JACC CardioOncol. 2020; 2(2): 293–311, doi: 10.1016/j.jaccao.2020.05.009, indexed in Pubmed: 34396236.
16. Chen TWW, Loong HH, Srikanthan A, et al. Primary cardiac sarcomas: A multi-national retrospective review. Cancer Med. 2019; 8(1): 104–110, doi: 10.1002/cam4.1897, indexed in Pubmed: 30575309.
17. Jumeau R, Vincenti MG, Pruvot E, et al. Curative management of a cardiac metastasis from lung cancer revealed by an electrical storm. Clin Transl Radiat Oncol. 2020; 21: 62–65, doi: 10.1016/j.ctro.2019.10.005, indexed in Pubmed: 31993511.
18. Bussani R, Castrichini M, Restivo L, et al. Cardiac Tumors: Diagnosis, Prognosis, and Treatment. Curr Cardiol Rep. 2020; 22(12): 169, doi: 10.1007/s11886-020-01420-z, indexed in Pubmed: 33040219.

VIA MEDICA

CASE REPORT

Mohsen Reza Mansoorian[1], **Shahriar Sabouri**[2]

[1]Department of General Surgery, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Surgery, Firoozgar Clinical Development Research Center (FCRDC), Iran University of Medical Sciences, Tehran, Iran

A case of a patient with embryonal sarcoma presenting with abdominal pain

Address for correspondence:
Dr. Shahriar Sabouri
Department of Surgery, Firoozgar Clinical Development Research Center (FCRDC), Iran University of Medical Sciences
Hemat Highway next to Milad Tower, 1449614535 Tehran, Iran
e-mail: shahriarsabouri85@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/ocp.95596

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Undifferentiated embryonal sarcoma of the liver is a rare and aggressive pediatric neoplasm. Due to its features in the imaging studies, there is a high rate of misdiagnoses. We present a 16-year-old female referred to our hospital with abdominal pain. At the initial work-up, we suspected a hydatid cyst as one of differential diagnoses due to the cystic pattern of the mass on the computed tomography scan. The needle biopsy smear was sent for pathology analysis which was negative for scolex of *Echinococcus granulosus*. However, the pathology report indicated neoplastic features in the biopsy. She underwent surgery and total resection was performed. The mass was sent for further investigation which confirmed the diagnosis of embryonal sarcoma with osteosarcomatous components. Embryonal sarcoma should be suspected in large tumors at any age.

Keywords: abdominal pain; sarcoma; case report

Oncol Clin Pract 2024; 20, 2: 148–151

Introduction

After hepatoblastoma and hepatocellular carcinoma, undifferentiated embryonal sarcoma (UES) is the third most prevalent primary malignant liver tumor in pediatrics. The majority of patients are between the ages of 6 and 10, without ethnic or sex predominance [1]. Stocker and Ishak described UES of the liver for the first time in 1978 [2]. It is mesenchymal in origin and rare in adults. Although UES is the third most frequent primary malignant tumor of the liver in the pediatric population, few cases have been reported in the literature. The presentation may include fever, weight loss, and pain. Additional signs and symptoms may include anorexia, vomiting, diarrhea, lethargy, constipation, and respiratory distress [1].

Here we report a case of a 16-year-old female who was admitted to our hospital with acute abdominal pain. We suspected the presence of a hydatid cyst as one of her differential diagnoses due to the cystic pattern of the mass on the computed tomography scan.

Case presentation

A 16-year-old girl was admitted to our hospital with complaints of progressive abdominal pain located in the right upper quadrant. It was her first presentation. On further inquiry, it turned out that she had no weight loss, was not febrile, or icteric. On physical examination, a huge, non-tender, and immobile liver was palpable in the right upper side of the abdomen. No palpable lymphadenopathy was detected, and her vital signs were within normal ranges. Laboratory tests showed normal liver function tests. Further examination was done. Computed tomography (CT) showed a well-defined low-density large heterogenous cystic lesion (190 × 115 × 163 mm) with solid components and

Received: 20.05.2023 Accepted: 28.08.2023 Early publication date: 30.11.2023

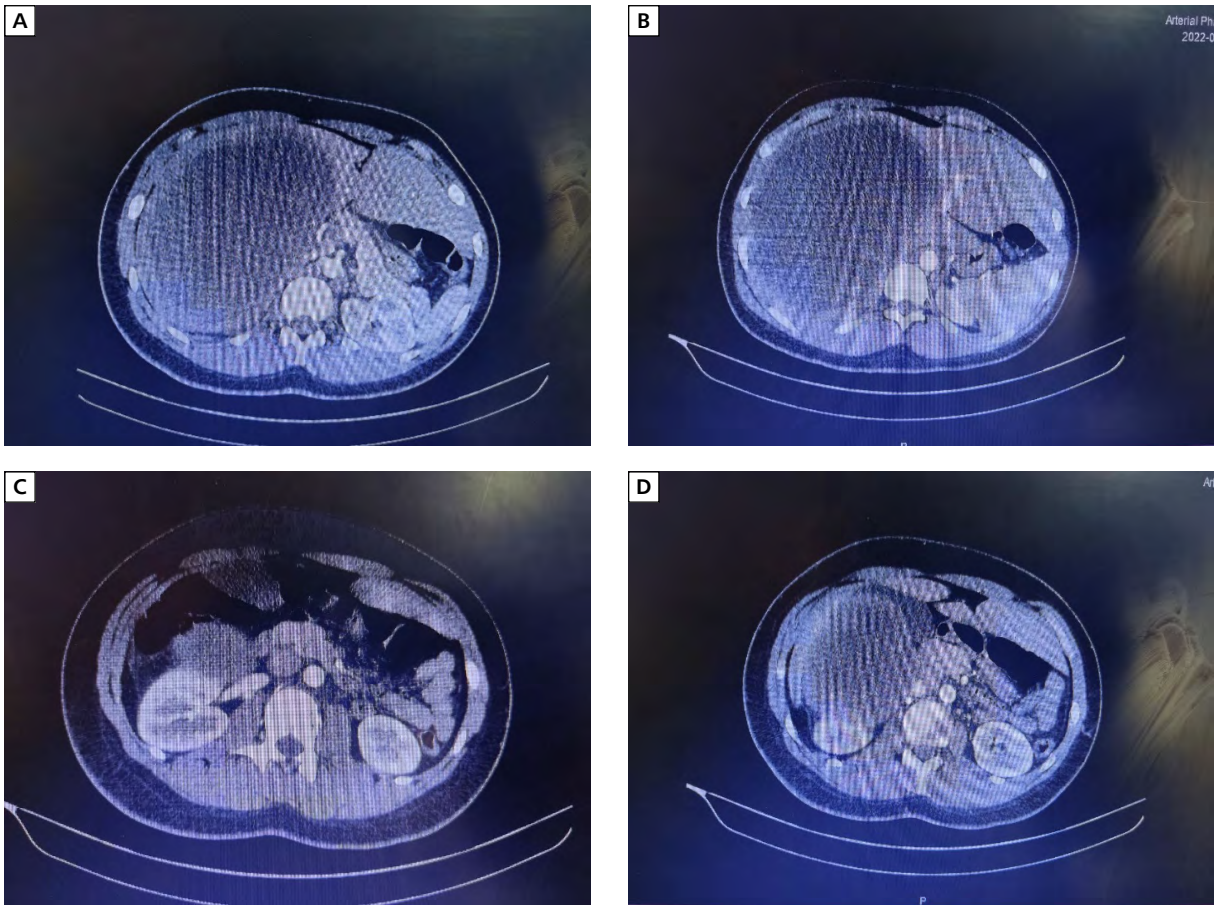

Figure 1A–D. Computed tomography scan showing a massive lesion in the liver: a well-defined low-density large heterogenous cystic lesion

enhanced septa in the right lobe of the liver (Fig. 1). On sonography, a huge solid cystic mass was seen in the right lobe of the liver. This massive mass had compressive effects on surrounding structures including the portal vein. Due to suspicion of hydatid cyst, the needle biopsy smear was sent for pathology examination which turned out to be negative for scolex of *Echinococcus granulosus.*

The biopsy pathology report indicated embryonal sarcoma with osteosarcomatous components. She underwent surgery with total resection of the tumor with nearly 2 cm tumor-free margins (Fig. 2). The right lobe of the liver, right biliary duct, and distal part of the duct were resected completely and sent for further histopathology investigation. It should be noted that due to the size of the mass and its highly compressive effect, the medical team decided that surgery was the best strategy because it seemed that chemotherapy would not be beneficial given the size of the mass.

Histopathology review documented malignant spindle cells and oval cells set in myoxid stroma. The cells had a high N/C ratio and hyperchromatic nuclei. Central necrosis and osteoid formation were also identified. On immunohistochemistry, CD10 was positive and SMA weakly scattered positive. After surgery, the patient was stable and was discharged with a follow-up treatment plan. She was followed up regularly, with no signs of recurrence on the last visit 10 months after surgery.

Discussion

Embryonal sarcoma of the liver is an aggressive mesenchymal tumor that occurs predominantly in pediatric patients. Despite years of research, the pathophysiology of this condition is still unknown. The prognosis for patients has been significantly improved by multimodal therapy, which includes surgery, chemotherapy, and radiation therapy. For better results, this successful management requires early diagnosis.

There are many possible diagnoses for undifferentiated liver embryonal sarcoma. Since each liver disease occurs in a certain age range, the patient's age

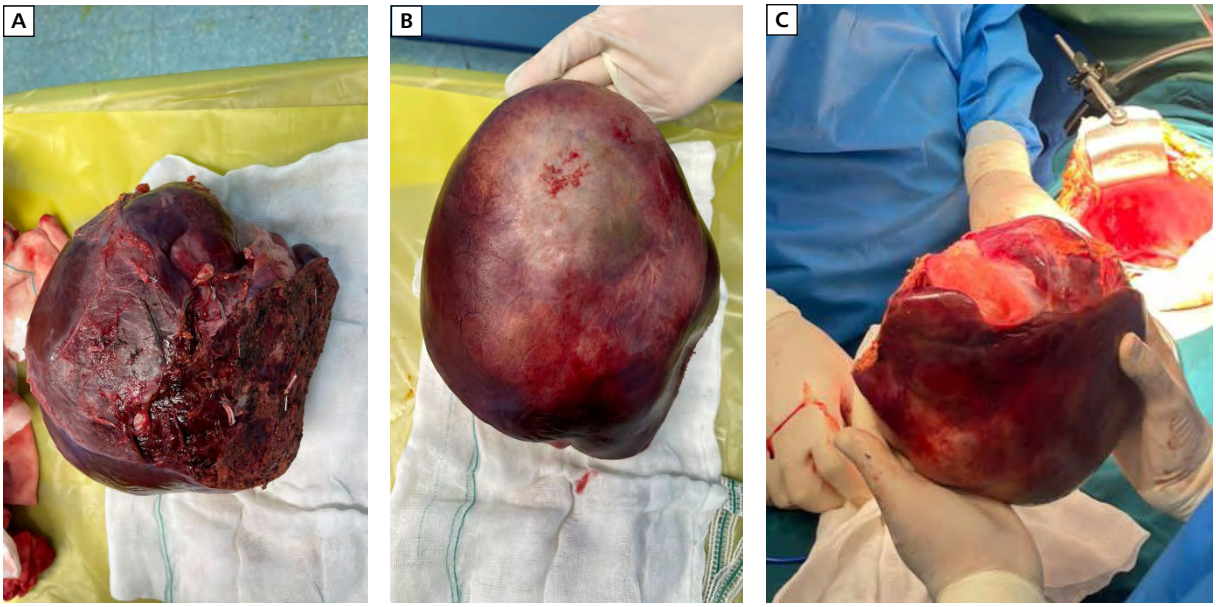

Figure 2A–C. The resected tumor

is frequently useful in reducing the number of possible differential diagnoses. However, our patient was older than the usual onset age. The UES of the liver is most often diagnosed in patients aged from 6 to 10 years.

In 2017, an 8-year-old male [3] had unsuccessful surgery for presumed hydatid disease which finally turned out to be UES of the liver located in the right lobe as in the case of our patient. Yoon et al. also reported a case of UES of the liver that was incidentally found in a 53-year-old female, which at first raised suspicion of a hydatid cyst. The follow-up CT scan suggested a neoplastic mass rather than a simple cyst [4].

Undifferentiated embryonal sarcoma of the liver is more frequent in the right lobe of the liver than in the left lobe [5]. After neuroblastoma and Wilms tumor, primary hepatic tumors are the third most common solid excrescences in pediatrics, accounting for approximately 2 percent of all pediatric cancers. Malignant mesenchymal hepatic tumors, hepatoblastoma and hepatocellular carcinoma, although rare, are very important in pediatrics [6].

The clinical features of UES are not specific. The signs and symptoms are usually related to the mass and its compressive effects on surrounding structures, as shown in this case. Palpable abdominal mass with or without upper abdominal pain may be found in some cases. Fever, which is found in the majority of tumors due to necrosis, hemorrhage, and cytokines effects, is not specific [7]. Undifferentiated embryonal sarcoma is not caused by cirrhosis or other chronic liver diseases; therefore, liver function tests and tumor markers including AFP, CEA, and CA19-9 are within normal limits in most cases.

Undifferentiated embryonal sarcoma is strongly positive for vimentin and 1-antitrypsin and focally positive for cytokeratin, desmin, αSMA, muscle-specific actin, CD68, myoglobin, neuron-specific enolase, S100, and CD34, which suggests that an embryonic sarcoma is undifferentiated.

In 2020, Zhang et al. [8] reviewed retrospectively all patients referred to the Shenging Hospital from 2005 to 2017 and recruited 14 patients aged 2 to 60. They indicated that the preoperative imaging had a high misdiagnosis rate, and total resection was the first treatment choice, as in our patient.

According to Techavichit et al. [9], total resection of the tumor mass combined with neoadjuvant chemotherapy with ifosfamide and doxorubicin, cyclophosphamide plus doxorubicin plus vincristine, or ifosfamide plus etoposide showed better survival outcomes in the case of localized resectable cancers. Furthermore, May et al. [10] recommended adjuvant chemotherapy as an alternative for these cases, using vincristine, actinomycin D, and cyclophosphamide (VAC) regimens. For patients with unresectable or advanced tumors, Techavichit et al. [9] recommended liver transplantation.

Undifferentiated embryonal sarcoma prognosis varies highly with survival ranging from 20 to 100 percent [9]. Techavichit et al. [9] and Zhang et al. [11] demonstrated that complete tumor resection is the key factor

in increasing the survival rate of patients with resectable UES tumors.

Due to the low prevalence of UES, misdiagnoses, such as hepatic abscess, hemorrhage cystic tumor, and hydatid cyst, are common [12].

Conclusions

Undifferentiated embryonal sarcoma should be considered in differential diagnosis of large liver tumors regardless of patients' age. Our case shows that early surgery can have the same results as a combination of chemotherapy and surgery to secure a better survival rate.

Article Information and Declarations

Ethics statement

All the performed procedures were in accordance with the ethical guidelines of Iran University of Medical Sciences and the Declaration of Helsinki 1975 (year 2008).

Written informed consent was obtained from the studied patient.

Author contributions

All authors were responsible for designing the study, collecting data, and writing the article.

Funding

None.

Acknowledgments

None.

Conflict of interest

The authors declare that there is no conflict of interest.

Supplementary material

None.

References

1. Putra J, Ornvold K. Undifferentiated embryonal sarcoma of the liver: a concise review. Arch Pathol Lab Med. 2015; 139(2): 269–273, doi: 10.5858/arpa.2013-0463-RS, indexed in Pubmed: 25611111.
2. Stocker JT, Ishak KG. Undifferentiated (embryonal) sarcoma of the liver: report of 31 cases. Cancer. 1978; 42(1): 336–348, doi: 10.1002/1097-0142(197807)42:1<336::aid-cncr2820420151>3.0.co;2-v, indexed in Pubmed: 208754.
3. Hashemieh MA. Case of Childhood Undifferentiated Embryonal Sarcoma of Liver Mimicking Hydatid Cyst. Iranian journal of Pediatric Hematology and Oncology. 2018; 8(4): 247–251.
4. Yoon JY, Lee JM, Kim DoY, et al. A case of embryonal sarcoma of the liver mimicking a hydatid cyst in an adult. Gut Liver. 2010; 4(2): 245–249, doi: 10.5009/gnl.2010.4.2.245, indexed in Pubmed: 20559529.
5. Pachera S, Nishio H, Takahashi Yu, et al. Undifferentiated embryonal sarcoma of the liver: case report and literature survey. J Hepatobiliary Pancreat Surg. 2008; 15(5): 536–544, doi: 10.1007/s00534-007-1265-y, indexed in Pubmed: 18836810.
6. Sakellaridis T, Panagiotou I, Georgantas T, et al. Undifferentiated embryonal sarcoma of the liver mimicking acute appendicitis. Case report and review of the literature. World J Surg Oncol. 2006; 4: 9, doi: 10.1186/1477-7819-4-9, indexed in Pubmed: 16504010.
7. Yedibela S, Reck T, Ott R, et al. [Undifferentiated, embryonal sarcoma as a rare cause of spontaneous liver rupture in adults]. Chirurg. 2000; 71(1): 101–105, doi: 10.1007/s001040051022, indexed in Pubmed: 10663012.
8. Zhang C, Jia CJ, Xu C, et al. Undifferentiated embryonal sarcoma of the liver: Clinical characteristics and outcomes. World J Clin Cases. 2020; 8(20): 4763–4772, doi: 10.12998/wjcc.v8.i20.4763, indexed in Pubmed: 33195644.
9. Techavichit P, Masand PM, Himes RW, et al. Undifferentiated Embryonal Sarcoma of the Liver (UESL): A Single-Center Experience and Review of the Literature. J Pediatr Hematol Oncol. 2016; 38(4): 261–268, doi: 10.1097/MPH.0000000000000529, indexed in Pubmed: 26925712.
10. May LT, Wang M, Albano E, et al. Undifferentiated sarcoma of the liver: a single institution experience using a uniform treatment approach. J Pediatr Hematol Oncol. 2012; 34(3): e114–e116, doi: 10.1097/MPH.0b013e3182331fbe, indexed in Pubmed: 22217489.
11. Zhang C, Jia CJ, Xu C, et al. Undifferentiated embryonal sarcoma of the liver: Clinical characteristics and outcomes. World J Clin Cases. 2020; 8(20): 4763–4772, doi: 10.12998/wjcc.v8.i20.4763, indexed in Pubmed: 33195644.
12. Shimagaki T, Sugimachi K, Mano Y, et al. Undifferentiated embryonal sarcoma of the liver occurring in an adolescent: a case report with genomic analysis. Surg Case Rep. 2022; 8(1): 170, doi: 10.1186/s40792-022-01528-0, indexed in Pubmed: 36107353.

VIA MEDICA

CASE REPORT

Aleksandra Łomża[1], Bernadeta Maliszewska[1], Łukasz Łaba[1], Izabela Chmielewska[2], Iwona Paśnik[3], Renata Langfort[4], Michał Gil[2], Paweł Krawczyk[2]

[1]Student Scientific Club at the Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland
[2]Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Poland
[3]Department of Clinical Pathomorphology, Medical University of Lublin, Poland
[4]Department of Pathomorphology, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

Immunochemotherapy in a 25-year-old male patient with small-cell lung cancer

Address for correspondence:
Izabela Chmielewska MD, PhD
Department of Pneumonology,
Oncology and Allergology,
Medical University of Lublin
ul. Jaczewskiego 8, 20–954 Lublin, Poland
e-mail: izabelachmielewska@umlub.pl

Oncology in Clinical Practice
DOI: 10.5603/ocp.97487

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Lung cancer is the leading cause of cancer-related deaths, both in males and females. Small-cell lung cancer (SCLC) is a strongly tobacco-dependent type of lung cancer characterized by aggressiveness, rapid growth, and a high tendency to metastasize. SCLC is the most commonly diagnosed in an advanced — metastatic — stage in patients with many comorbidities and inadequate performance status. However, based on the most current recommendations, chemotherapy in combination with immunotherapy at the extensive stage (ES) of SCLC, significantly improves the therapeutic efficiency. Here, we present a case of a 25-year-old man, diagnosed with SCLC, with a medical history of 10 years of smoking e-cigarettes and marijuana as well as the use of amphetamine and alcohol. In the diagnosis process, considering the young age of the patient, the next-generation sequencing (NGS) was performed, but no molecular alterations in oncogenes were found. During the immunochemotherapy with atezolizumab, carboplatin, and etoposide, immune-related adverse events (irAEs), in the form of hepatotoxicity, were observed. After the toxicity subsided, the immunotherapy was continued with a very good effect and tolerance. The patient has remained in partial remission for 9 months. The presented case highlights the possibility of treatment continuation despite mild adverse events triggered by immunotherapy and the need for more research in the group of young patients diagnosed with SCLC.

Keywords: immunotherapy, immune-related adverse events, small-cell lung cancer, toxicity

Oncol Clin Pract 2024; 20, 2: 152–159

Introduction

Small-cell lung cancer (SCLC) accounts for 10-15% of all lung cancer diagnoses worldwide [1]. It is characterized by a high proliferative rate and a strong tendency for early dissemination. Despite many years of research, the prognosis for SCLC is poor. It is recommended to classify the disease stage based on the TNM system (T — size of the primary tumor, N — regional lymph nodes that are involved, M — distant metastasis) [5]. However, SCLC is traditionally graded, based on the possibility of using radiotherapy, into a limited stage (LS) and an extensive stage (ES) [2]. Consequently, most patients (60–70%) have the ES of disease at the time of diagnosis — they are diagnosed when cancer extends outside the ipsilateral lung and regional lymph nodes, which cannot be covered by a single field of irradiation [3]. Treatment of LS SCLC consists of chemotherapy and radiotherapy, and this therapy can cure 20–25% of patients. Patients with ES SCLC have poor prognosis, but immunochemotherapy can improve quality of life and overall survival [4].

Received: 18.09.2023 Accepted: 27.09.2023 Early publication date: 27.10.2023

Case report

In November 2022, a 25-year-old man was hospitalized in the Department of Pneumonology, Oncology and Allergology for a mediastinal tumor detected on his chest X-ray. The chest imaging examination was performed because of hemoptysis and suspected rib injury. During the diagnostics, the patient developed paraneoplastic hyponatremia. The patient's medical history included the use of stimulants of unknown origin (10 pack-years), marijuana, amphetamine, and alcohol abuse. In the family history, maternal thyroid cancer was disclosed. During hospitalization, chest computed tomography (CT) was performed, which revealed fluid in the right pleural cavity and a tumor of the lower lobe of the right lung with peripheral atelectasis. The tumor was connected with enlarged lymph nodes forming a pathological mass in the subcarinal cavity and in the right hilum, as well as enlarged lymph nodes of the left hilum and aortopulmonary window. The tumor was compressing the left atrium, tracheal carina, and lobar bronchi. It adhered to the aorta and esophagus, modeling the vessels in this area.

Bronchoscopy with endobronchial ultrasound transbronchial needle aspiration biopsy (EBUS-TBNA) was performed, and it revealed right-sided narrowing of the middle lobe bronchus and external compression of the right seventh segment bronchus. In-depth (due to an unusual case) pathomorphological examination of the tumor material was performed. Slides stained with hematoxylin and eosin showed a confluent infiltrate of small monotonous tumor cells. Immunohistochemical (IHC) staining was performed (Fig. 1). The expression of the following markers was found: CK AE1/AE3 (cytokeratin, weak, perinuclear), TTF1 (thyroid transcription factor 1, strong in 100% of tumor cells), chromogranin A (perinuclear) and synaptophysin (positive), FLI-1 (friend leukemia integration-1, positive), CD56 (positive), NSE (neuron-specific enolase, focal), Ki67 (strong in 90% of tumor cells), while p40, CD45, CD99, and nuclear protein of the testis (NUT) were not expressed. Low-grade neuroendocrine carcinoma (small-cell lung cancer) was diagnosed. The diagnosis of NUT midline carcinoma, primitive neuroectodermal tumor (PNET), and Ewing sarcoma was taken into account in the diagnosis.

Next-generation sequencing (NGS) is not a standard procedure in SCLC patients, but it was performed due to the very young age of the patient and unknown thyroid cancer in the family. We used the Ion Torrent S5 sequencer and the Oncomine Focus test (Thermo Fisher Scientific, US), which enable the examination of mutations, rearrangements, and copy number changes in 52 oncogenes. However, no oncogenic mutations were detected. Based on the tests carried out, the final diagnosis of small-cell carcinoma at the T4N2M1a stage was established.

By the decision of the multidisciplinary tumor board, the patient was qualified for immunochemotherapy with carboplatin, etoposide, and atezolizumab. After the fourth cycle of immunochemotherapy, hepatotoxicity manifested by an increase in bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels (Fig. 2) was observed as well as yellowing of the sclera. Grade 1 liver failure was diagnosed and, for this reason, the administration of subsequent cycles of immunotherapy was postponed. Systemic steroid therapy was not implemented.

After stabilization of the liver parameters, the treatment was continued with good tolerance. A follow-up CT examination showed partial response: a decrease in the size of the tumor of the lower lobe of the right lung, subcranial lymph nodes, right and left hilar lymph nodes, and a decrease in the amount of fluid in the right pleural cavity. Partial remission is maintained (Fig. 3). Currently (September 2023), the patient is in better general condition, with no report of any side effects or complications of the treatment.

Discussion

Fewer than 5% of SCLC patients achieve the 5-year survival rate. The majority of patients survive less than 1 year after diagnosis [6]. Small-cell lung cancer is characterized by an early relapse, and about one-third of relapsed patients have brain metastases. Slotman et al. showed that prophylactic cranial irradiation (PCI) may reduce the prevalence of brain secondary deposits and increase overall survival (OS) in SCLC patients [7]. Therapeutic options for SCLC patients are limited. Surgical treatment does not affect OS, and it is an option only for TNM stage I (T1-2N0M0) patients with no mediastinal or supraclavicular lymph node metastases. The first-line treatment for ES SCLC patients is a combination of cisplatin or carboplatin and etoposide. Nonetheless, median of OS for ES SCLC patients treated with standard chemotherapy is only approximately 10 months [8]. The newly recommended standard of treatment in ES SCLC patients consists of immunotherapy combined with chemotherapy. Results of two important phase III clinical trials (IMpower133 and CASPIAN) have shown a significant role of the combination of immune checkpoint inhibitors (ICIs) with first-line chemotherapy in the treatment of ES SCLC patients [9].

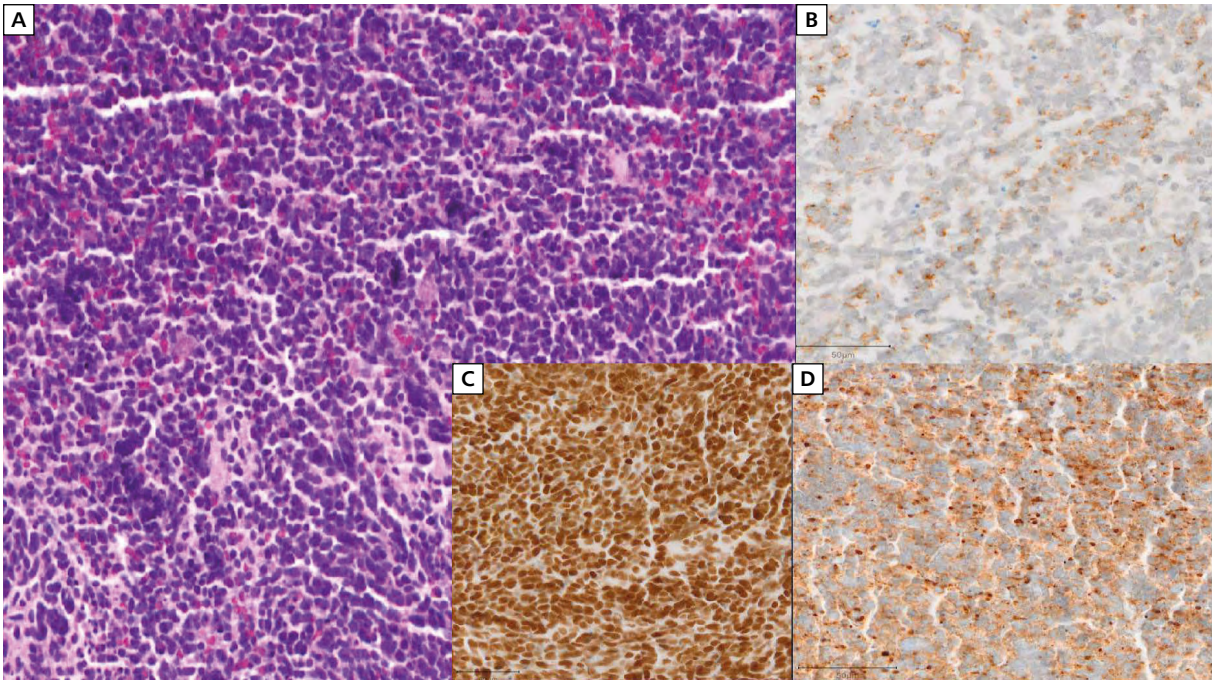

Figure 1. A. Diffuse tumor infiltration of small cells with scant cytoplasm. H + E stain. High magnification. Microphotograph; **B.** Weak, focal reaction with keratin in some neoplastic cells. Keratin AE1/AE3 stain. High magnification. Microphotograph; **C.** The tumor cells stain strongly for thyroid transcription factor-1 (TTF-1). TTF-1 immunohistochemical stain. High magnification. Microphotograph; **D.** Medium intense reaction with chromogranin A. Chromogranin A reaction. High magnification. Microphotograph

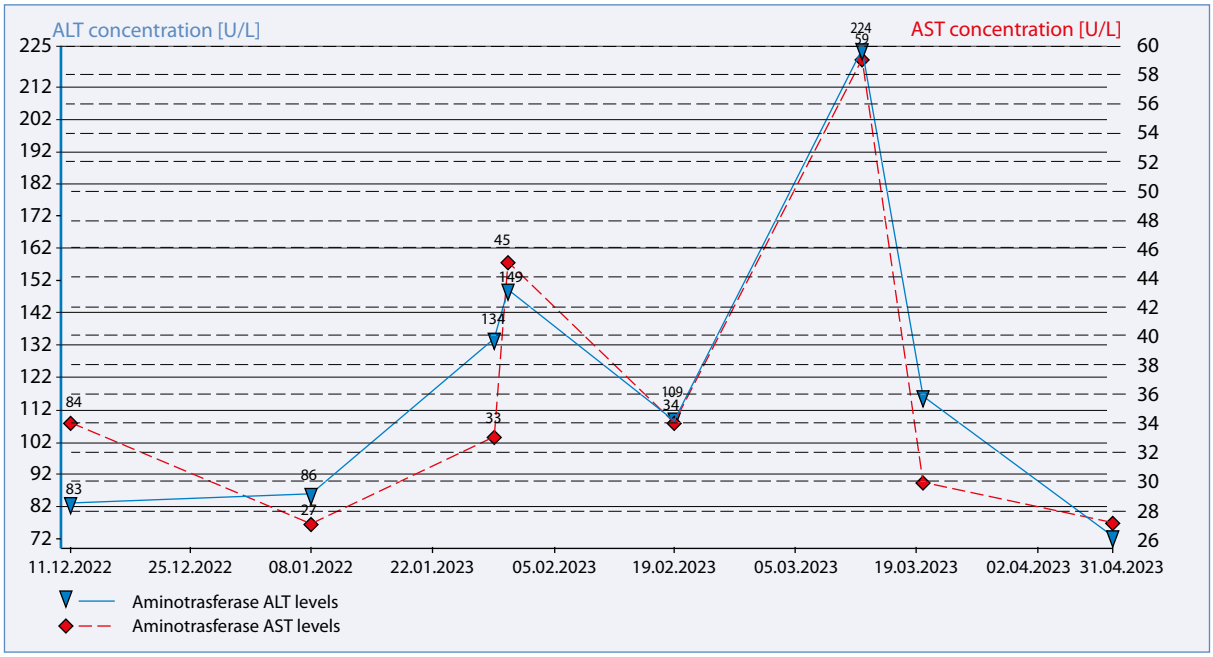

Figure 2. Graphic presentation of a treatment-related increase in the levels of aminotransferases; ALT — alanine aminotransferase; AST — aspartate aminotransferase

IMpower133

Atezolizumab is a humanized monoclonal antibody anti-programmed death ligand (anti-PD-L1) that inhibits the binding of PD-L1 to the PD-1 receptor on lymphocytes [10]. The IMpower133 study evaluated the safety and efficacy of using atezolizumab or placebo in addition to first-line chemotherapy treatment with

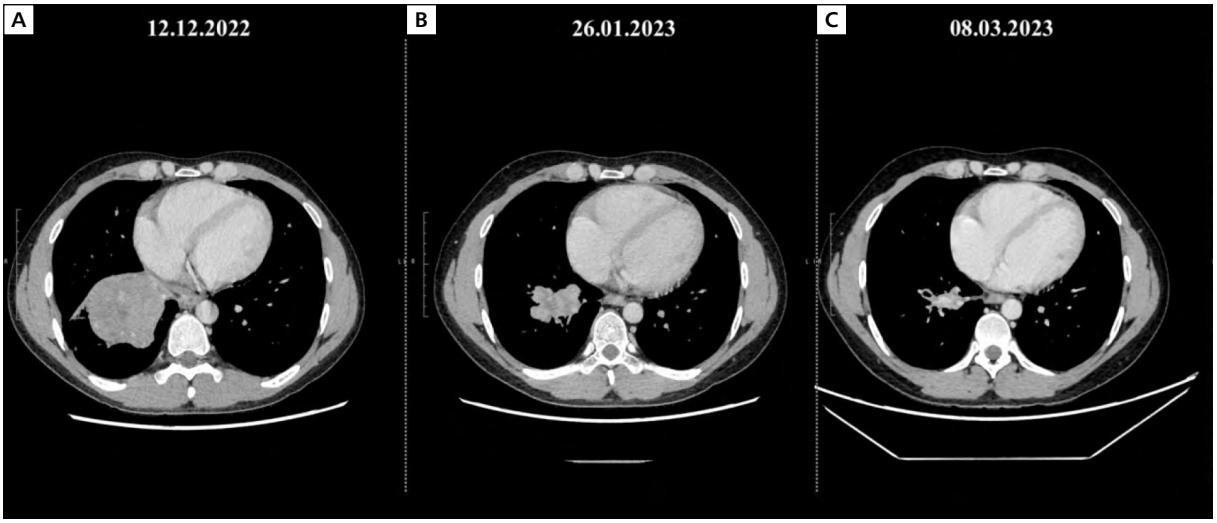

Figure 3A–C. Regression of the tumor shown in three consecutive computed tomography scans

carboplatin and etoposide (CP/ET) in ES SCLC patients [11]. This clinical trial recruited 403 patients who were randomly assigned into two groups (placebo plus CP/ET *vs.* atezolizumab plus CP/ET). Results showed that median OS in patients who received atezolizumab plus CP/ET was two months longer than in patients who received only CP/ET (12.3 months *vs.* 10.3 months, HR = 0.70; 95% CI 0.54–0.91; p = 0.0096). Median progression-free survival (PFS) of patients who received atezolizumab plus CP/ET was one month longer than un the case of patients who received only CP/ET (5.2 months *vs.* 4.3 months, HR = 0.77; 95% CI 0.62–0.96; p = 0.017). After 18 months of follow-up, 34.0% of patients were alive in the atezolizumab plus CP/ET group, and 21.0% of patients in the placebo plus CP/ETgroup [11, 12].

CASPIAN

Durvalumab is a humanized monoclonal anti-PD-L1 antibody [13]. The CASPIAN study examined the efficacy and safety of durvalumab added to first-line platinum (carboplatin or cisplatin) based chemotherapy with etoposide (P/ET) in ES SCLC patients. All 805 patients were randomly assigned to one of three groups: durvalumab plus P/ET, durvalumab plus tremelimumab (monoclonal antibody anti-CTLA-4, cytotoxic T lymphocyte antigen 4) plus P/ET and only P/ET [14]. The study reported the following results – median OS in the durvalumab plus P/ET group, in comparison to only P/ET, was extended by 2 months (12.9 months *vs.* 10.5 months, HR = 0.71; 95% CI 0.60–0.86; p = 0.0003). The two-year OS rate in the durvalumab plus P/ET group, compared to only P/ET group, was 22.9% *vs.* 13.9%, and the three-year OS rate in the durvalumab plus P/ET group, compared to the only P/ET group, was 17.6% *vs.* 5.8%. Furthermore, the rate of serious adverse events (SAEs) in the durvalumab plus P/ET group, compared to the only P/ET group, was 32.5% *vs.* 36.5% [12, 14].

Immunochemotherapy with atezolizumab or durvalumab in addition to first-line chemotherapy in ES SCLC patients resulted in a significant improvement in OS rates. Both studies have shown that atezolizumab and durvalumab had remarkable efficacy and favorable safety in ES SCLC patients [12].

Based on the decision of the Ministry of Health, atezolizumab immunotherapy combined with first-line chemotherapy (CP/ET) is reimbursed in Poland for patients with ES SCLC. In March 2023, durvalumab in combination with first-line chemotherapy (P/ET) was added to the program. Moreover, patients with ES SCLC and controlled central nervous system metastases can receive immunochemotherapy.

Toxicity of immunotherapy

The immunotherapy mechanism is to activate, expand, or redirect tumor-reactive T cells to increase cell anti-tumor immune responses. Immunotherapy apart from prolonging survival of patients with SCLC and many other cancers, may cause side effects. Among important complications are immune-related adverse events (irAEs) as a result of treatment-induced inflammation, which most commonly affects the skin, liver, digestive tract, and the endocrine system [15]. Hepatotoxicity induced by immunotherapy can range from a moderate increase of liver aminotransferases

Table 1. Management of immune-related hepatotoxicity according to the European Society for Medical Oncology (ESMO) recommendations and summary of product characteristics for durvalumab

Severity of symptoms	Assessment of investigations	Treatment modification and corticosteroid therapy
ALT or AST > ULN to 3 × ULN	• Monitor liver enzymes every 1–2 weeks	• Continue ICI therapy
ALT or AST 3–5 × ULN	• Check LFTs, INR, and albumin twice weekly • Test hepatitis B, C, and E (sometimes A) • Examine PCR, anti-ANA, SMA, LKM, SLA/LP, LCI, and iron levels • Review history of medications and alcohol • Consider imaging metastases and/or clot	• Withhold ICI therapy • Avoid hepatotoxic drugs • In the case of rising ALT and/or AST, start administration of corticosteroids 0.5–1 mg/kg/day • In the case of improvement, resume ICI therapy after tapering corticosteroids to < 10 mg/day • In the case of no improvement, discontinue ICI therapy and increase the dose of corticosteroids to 1–2 mg/kg/day
ALT or AST 5–20 × ULN	• Check LFTs, INR, and albumin daily • Imaging tests of the liver: US, CT, or MRI • Consider hepatologist consultation and/or liver biopsy	• Discontinue ICI therapy • If ALT and/or AST < 400U/l with normal INR, bilirubin, and albumin, start administration of cortcosteroids 1–2 mg/kg/day • If ALT and/or AST > 400 U/l with raised INR/bilirubin and low albumin, start administration of methylprednisolone 2 mg/kg i.v.
ALT or AST > 20 × ULN	As above	• Discontinue ICI therapy • Start administration of methylprednisolone 2 mg/kg i.v.
According to the summary of product characteristics for durvalumab		
• In the case of concomitance ALT or AST > 3 × ULN and total bilirubin > 2 × ULN — discontinue ICI therapy and start administration of prednisone 1–2 mg/kg/day or its counterpart and then reduce the dose • In the case of ALT or AST > 10 ULN or total bilirubin > 3 × ULN — discontinue ICI therapy and start administration of prednisone 1–2 mg/kg/day or its counterpart and then reduce the dose		

ALT — alanine aminotransferase; AST — aspartate aminotransferase; CT — computed tomography; ICI — immune checkpoint inhibitor; MRI — magnetic resonance imagining

and hyperbilirubinemia to, exceptionally, fulminant liver failure. Hepatotoxicity caused by ICIs may be clinically asymptomatic. However, symptoms such as fever, jaundice, fatigue, and maculopapular rash have been reported. During the diagnostic process, it is important to rule out other etiologies of hepatotoxicity. Management of hepatotoxicity usually includes cessation of immunotherapy and application of corticosteroids or other immunosuppressive agents. Most patients can restart the immunotherapy after recovery [16, 17]. Specific recommendations of the European Society for Medical Oncology (ESMO) for management of hepatotoxicity due to immunotherapy depend on symptom grade. Recommendations are also presented by ICI producers (Tab. 1) [18].

Small-cell lung cancer in young patients

Although lung cancer is most commonly diagnosed in older patients, there are patients with the diagnosis at a young age. Patients with non-small cell lung cancer (NSCLC) under the age of 30 are quite noften described in the literature. Such patients usually have single-driver alterations in oncogenes, e.g. in the *EGFR* (epidermal growth factor receptor), *ALK* (anaplastic lymphoma kinase), or *ROS1* (ROS1 protoncogene) genes. The literature presented a profile of younger NSCLC patients diagnosed with lung cancer. They are most frequently females with no smoking history and an advanced stage of disease. Young NSCLC patients have better OS only in early stages of the disease (I or II) when resection is

possible. However, the prognosis of patients with advanced NSCLC and with genetic alteration has also recently improved with the use of molecularly targeted therapies [19].

Small-cell lung cancer patients under the age of 30 are extremely rarely described (the cause of SCLC is most often long-term exposure to tobacco smoke). Otherwise, previous studies of SCLC suggested poor prognosis regardless of the patient's age. Lee et al. [20] found that young patients diagnosed with SCLC, despite being healthier than older patients and having no comorbidities, presented adverse survival outcomes, especially in those with extensive stages of cancer. Chemoimmunotherapy may change the prognosis in this group of patients, as evidenced by the effectiveness of this method of treatment in our patient.

There is a description of a similar case in the literature. A case of a 22-year-old patient with a final diagnosis of SCLC who had smoked one marijuana joint three times a week for three years but did not smoke cigarettes. Although rare, it should alert physicians that cannabis smoking may be a risk factor for lung cancer [21]. Further investigations in young patients diagnosed with SCLC are warranted to understand and determine age- and treatment-related factors to improve survival rates in this group.

E-cigarettes and the respiratory system

Electronic cigarettes (e-cigarettes) are non-combustible tobacco products that contain nicotine, and liquid propylene glycol and vegetable glycerin flavorings. The e-cigarette liquid is first heated, by using a battery-powered device and then inhaled as an aerosol [22]. E-cigarettes are considered an alternative to help patients struggling with smoking cessation [23]. Although e-cigarettes avoid the release of tarry substances, they still emit heavy metals, furans, volatile carbonyls, and reactive oxygen species. Moreover, e-liquids may contain much more toxic substances because the e-cigarette market is not well controlled by government organizations. E-cigarette users may have access to e-liquids of unknown origin or they may modify the composition of e-liquids themselves (e.g. by adding cannabinoids and solvents such as tocopherol — vitamin E).

Using e-cigarettes, called "vaping", significantly influences the pulmonary system, by downregulation of immune genes in the nasal epithelia, inhibiting ciliary beating, and enhancement of proinflammatory cytokine secretion in the bronchial epithelia. Additionally, e-cigarettes affect sputum by impaired macrophage function, increased levels of MUC5AC mucin and proteases, and bronchial endothelia by impaired vasoconstriction and increased bronchial wall stiffness. These processes may lead to mild chronic respiratory inflammation and injuries in the small airways. [24]. Respiratory tissue exposed via epithelium metaplasia, injuries and, indirectly, by chronic inflammation may be prospective areas for oncogenesis. Directly, e-cigarettes and vaping fluids contain nicotine derivatives and other organic compounds (polycyclic aromatic hydrocarbons, benzene, amines), which are defined as potential carcinogens [25]. Schall et al. [26] discovered that nicotine and e-cigarette components can promote the self-renewal of lung adenocarcinoma stem-like cells. The molecular and genetic pathways described the activation of transcription factors Oct4, Yap1, and E2F1 in response to signaling events from the α7 nAChR. Hence, the growth of lung adenocarcinoma is perhaps promoted by nicotine and e-cigarettes [26].

The relationship between the use of e-cigarettes and the development of lung cancer, including SCLC, at a young age has not yet been described. Our patient may be the first such case in the literature although the association of vaping and smoking marijuana with SCLC development in our patient is uncertain. However, the toxicity of e-liquids has already been well documented. Due to the widespread use of e-cigarettes, a new disease entity has been described. E-cigarette or vaping product use-associated lung injury (EVALI) is an acute lung injury associated with the use of electronic cigarettes, which may be severe and lead to death. The mortality rate is 2.4%. Most patients (up to 94%) diagnosed with the disease used e-liquids containing tetrahydrocannabinoids (THC) and high concentrations of tocopherol. The most common symptoms of EVALI are shortness of breath and cough. Approximately half of patients experience chest pain and sometimes they have hemoptysis. Common gastrointestinal symptoms are nausea, vomiting, diarrhea, and abdominal pain. Most patients experience fever, chills, and weakness. Infiltrative changes in the lungs and ground glass opacities in chest CT are characteristic. EVALI treatment involves high doses of glucocorticosteroids, antibiotic therapy, oxygen therapy, and in severe cases, respiratory therapy [27, 28].

Another concern is various e-cigarettes technologies with different nicotine exposure, flavorings, coil power, atomizer construction, and lack of general recommendations. Furthermore, electronic vaporization of nicotine causes the same addictive behaviors as nicotine in traditional cigarettes and promotes nicotine dependence [24]. In conclusion, e-cigarettes cannot be a tool helping patients with smoking cessation. Based on presented histological and molecular changes induced by vaping in multiple lung regions, there is concern about long-term consequences caused by e-cigarettes and their likely toxicity, which are currently being investigated.

Conclusions

Results from two important phase III clinical trials, IMpower133 and CASPIAN, have shown that immunotherapy combined with chemotherapy offers the hope of prolonging OS in patients with ES SCLC, compared with standard first-line chemotherapy. Although immunotherapy may cause many complications — an example is hepatotoxicity that was diagnosed in our patient. The diagnosis of SCLC, especially in young patients, requires extensive clinical review to select an appropriate treatment. There is a need for large population studies to define the molecular signature and clinical management of SCLC and improve treatment outcomes in young patients. More research is also necessary to inspect and prevent the consequences of immune checkpoint inhibitor treatment.

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.

Author contributions

A.Ł: methodology, investigation, writing — original draft; B.M.: writing — original draft; Ł.Ł.: writing — original draft; I.C.: conceptualization, writing, review and editing; I.P., R.L., M.G.: methodology; P.K.: conceptualization, review and editing.

Funding

None.

Acknowledgments

None.

Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

References

1. Torre LA, Siegel RL, Ward EM, et al. Global Cancer Incidence and Mortality Rates and Trends-An Update. Cancer Epidemiol Biomarkers Prev. 2016; 25(1): 16–27, doi: 10.1158/1055-9965.EPI-15-0578, indexed in Pubmed: 26667886.
2. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging. 2012; 11(1): 253–258, doi: 10.1102/1470-7330.2011.0036, indexed in Pubmed: 22245990.
3. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017; 17(12): 725–737, doi: 10.1038/nrc.2017.87, indexed in Pubmed: 29077690.
4. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer. 2015; 121(5): 664–672, doi: 10.1002/cncr.29098, indexed in Pubmed: 25336398.
5. Memmott RM, Wolfe AR, Carbone DP, et al. Predictors of Response, Progression-Free Survival, and Overall Survival in Patients With Lung Cancer Treated With Immune Checkpoint Inhibitors. J Thorac Oncol. 2021; 16(7): 1086–1098, doi: 10.1016/j.jtho.2021.03.017, indexed in Pubmed: 33845212.
6. Wang Y, Zou S, Zhao Z, et al. New insights into small-cell lung cancer development and therapy. Cell Biol Int. 2020; 44(8): 1564–1576, doi: 10.1002/cbin.11359, indexed in Pubmed: 32281704.
7. Slotman B, Faivre-Finn C, Kramer G, et al. EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007; 357(7): 664–672, doi: 10.1056/NEJMoa071780, indexed in Pubmed: 17699816.
8. Hou J, Li H, Ma S, et al. Emerging therapies for small cell lung cancer. J Hematol Oncol. 2019; 12(1): 47, doi: 10.1186/s13045-019-0736-3, indexed in Pubmed: 31046803.
9. El Sayed R, Blais N. Immunotherapy in Extensive-Stage Small Cell Lung Cancer. Curr Oncol. 2021; 28(5): 4093–4108, doi: 10.3390/curroncol28050347, indexed in Pubmed: 34677265.
10. Liu SV, Reck M, Mansfield AS, et al. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol. 2021; 39(6): 619–630, doi: 10.1200/JCO.20.01055, indexed in Pubmed: 33439693.
11. Horn L, Mansfield AS, Szczęsna A, et al. IMpower133 Study Group. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018; 379(23): 2220–2229, doi: 10.1056/NEJMoa1809064, indexed in Pubmed: 30280641.
12. Liu X, Xing H, Liu B. Current status and future perspectives of immune checkpoint inhibitors in extensive-stage small cell lung cancer. Am J Cancer Res. 2022; 12(6): 2447–2464, indexed in Pubmed: 35812062.
13. Lin S, Luo S, Gu D, et al. First-Line Durvalumab in Addition to Etoposide and Platinum for Extensive-Stage Small Cell Lung Cancer: A U.S.-Based Cost-Effectiveness Analysis. Oncologist. 2021; 26(11): e2013–e2020, doi: 10.1002/onco.13954, indexed in Pubmed: 34431578.
14. Paz-Ares L, Dvorkin M, Chen Y, et al. CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019; 394(10212): 1929–1939, doi: 10.1016/S0140-6736(19)32222-6, indexed in Pubmed: 31590988.
15. Autio KA, Boni V, Humphrey RW, et al. Probody Therapeutics: An Emerging Class of Therapies Designed to Enhance On-Target Effects with Reduced Off-Tumor Toxicity for Use in Immuno-Oncology. Clin Cancer Res. 2020; 26(5): 984–989, doi: 10.1158/1078-0432.CCR-19-1457, indexed in Pubmed: 31601568.
16. Da Cunha T, Wu GY, Vaziri H. Immunotherapy-induced Hepatotoxicity: A Review. J Clin Transl Hepatol. 2022; 10(6): 1194–1204, doi: 10.14218/JCTH.2022.00105, indexed in Pubmed: 36381098.
17. Swanson LA, Kassab I, Tsung I, et al. Liver injury during durvalumab-based immunotherapy is associated with poorer patient survival: A retrospective analysis. Front Oncol. 2022; 12: 984940, doi: 10.3389/fonc.2022.984940, indexed in Pubmed: 36353563.
18. Haanen J, Obeid M, Spain L, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022; 33(12): 1217–1238, doi: 10.1016/j.annonc.2022.10.001, indexed in Pubmed: 36270461.
19. Arnold BN, Thomas DC, Rosen JE, et al. Lung Cancer in the Very Young: Treatment and Survival in the National Cancer Data Base. J Thorac Oncol. 2016; 11(7): 1121–1131, doi: 10.1016/j.jtho.2016.03.023, indexed in Pubmed: 27103511.
20. Lee MH, Qureshi MM, Suzuki K, et al. Small cell lung cancer in young patients: trends in sociodemographic factors, diagnosis, treatment, and survival. J Thorac Dis. 2022; 14(8): 2880–2893, doi: 10.21037/jtd-22-210, indexed in Pubmed: 36071763.
21. Kothadia JP, Chhabra S, Marcus A, et al. Anterior mediastinal mass in a young marijuana smoker: a rare case of small-cell lung cancer. Case Rep Med. 2012; 2012: 754231, doi: 10.1155/2012/754231, indexed in Pubmed: 22545056.
22. Herman M, Tarran R. E-cigarettes, nicotine, the lung and the brain: multi-level cascading pathophysiology. J Physiol. 2020;

598(22): 5063–5071, doi: 10.1113/JP278388, indexed in Pubmed: 32515030.
23. Cummings KM, Dresler CM, Field JK, et al. E-cigarettes and cancer patients. J Thorac Oncol. 2014; 9(4): 438–441, doi: 10.1097/JTO.0000000000000129, indexed in Pubmed: 24736063.
24. Gotts JE, Jordt SE, McConnell R, et al. What are the respiratory effects of e-cigarettes? BMJ. 2019; 366: l5275, doi: 10.1136/bmj.l5275, indexed in Pubmed: 31570493.
25. Bracken-Clarke D, Kapoor D, Baird AM, et al. Vaping and lung cancer - A review of current data and recommendations. Lung Cancer. 2021; 153: 11–20, doi: 10.1016/j.lungcan.2020.12.030, indexed in Pubmed: 33429159.
26. Schaal CM, Bora-Singhal N, Kumar DM, et al. Regulation of Sox2 and stemness by nicotine and electronic-cigarettes in non-small cell lung cancer. Mol Cancer. 2018; 17(1): 149, doi: 10.1186/s12943-018-0901-2, indexed in Pubmed: 30322398.
27. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. Lancet Respir Med. 2019; 7(12): 1017–1026, doi: 10.1016/S2213-2600(19)30415-1, indexed in Pubmed: 31711871.
28. Rice SJ, Hyland V, Behera M, et al. Guidance on the Clinical Management of Electronic Cigarette or Vaping-Associated Lung Injury. J Thorac Oncol. 2020; 15(11): 1727–1737, doi: 10.1016/j.jtho.2020.08.012, indexed in Pubmed: 32866653.