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ORIGINAL ARTICLES

REVIEW ARTICLES

CASE REPORTS

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

Case Report Contest Policies

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

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ORIGINAL ARTICLE

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Supportive activities in oncological wards during the COVID-19 pandemic: a qualitative study

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ABSTRACT

Introduction. The oncology ward is a challenging and unique workplace due to physical and psychological stress that staff experience and the need for their support. Cancer patients and oncology nurses have many needs, and support is one of the basic ones. This study aimed to explore supportive activities in the oncology ward during the COVID-19 pandemic.

Material and methods. This qualitative study was conducted in Eastern and Southeastern Iran in 2020 and 2021 through a conventional content analysis approach. The participants included 21 (10 oncology nurses, 5 managers, and 6 cancer patients), who were selected through purposive sampling. To collect data, in-depth semi-structured face-to-face interviews were done. Interviews were continued until data saturation was achieved. After transcribing the interviews, the data were analyzed according to the steps proposed by Graneheim & Lundman.

Results. The results consisted of three main themes and nine categories, namely the perceive of threat in supportive atmosphere in the oncology ward (cancer patients' sense of desperation and need for support, difficulty of working in the department, close relationships governing the ward), Seeking support in the oncology ward (Professional support, patient advocacy), and supportive divergence (poor family support, perceived poor social support, unsupportive behaviors, Being far from the supportive standards of working in an oncology ward).

Conclusions. The results of the study have shown that the supportive activities in the oncology ward during the COVID-19 pandemic are affected by various factors. The experiences of participants provide new insight into supportive activities around managing oncology wards supportive needs during such stressful times.

Key words: COVID-19, Iran, social support, neoplasms, stress, psychological atmosphere

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Introduction

Coronavirus disease 2019 (COVID-19) is a major public health problem worldwide. The World Health Organization (WHO) on March 11, 2020, declared the COVID-19 outbreak a global pandemic [1]. According to the latest reports on January 4, 2022, there are more than 292,652,910 COVID-19 patients and 5,465,344 confirmed deaths due to COVID-19 in the world [2]. Cancer patients are more vulnerable to COVID-19 than other groups due to systemic immunodeficiency. The vulnerability of cancer patients to COVID-19 leads to delaying or stopping cancer treatment to avoid the risk of potential COVID-19 exposure [3]. During this pandemic, due to the greater vulnerability of cancer patients, they need support more than before. This support includes support from a health worker, effective communication, assistance from relief organizations [4]. As mentioned, supporting cancer patients is very important so the patient is able to live with cancer [5].

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Nurses use their skills to support roles patients [6]. Patient support is one of the basic concepts in nursing care [7]. The oncology ward is a challenging and unique workplace for nurses due to the physical and psychological stress that cancer patients face. In addition, nurses require high functional skills to care for cancer patients and provide psychological support to the patients and their families [8].

On the other hand, the outbreak of COVID-19 has created many problems for nurses in hospitals, including fatigue [9]. Nurses are expected to provide quality care by supporting their patients despite limitations in the organizational structure [10]. Managers can also be involved in supporting their employees and managing job stress through some measures, such as guiding and supporting employees, designing an appropriate and motivational legal system, involving individuals in decision making, and improving organizational relationships [11].

Toh et al. [12] also consider nursing managers as the main sources of support and believe that the support of nursing managers leads to better job performance and the prevention of burnout. Martinussen and Davidsen [13] have reported that managers' support for nursing staff plays a key role in their productivity because nurses are more involved in cancer patient care than other health care providers and have a pivotal role in supporting patients and their families [14].

Thus, with the outbreak of the COVID-19 pandemic, supporting cancer patients can be helpful for patients to cope with their stress. However, the findings of related research have indicated a lack of nurses and physicians' support for patients or that some patients do not find the support received to be beneficial [15]. The review of the literature has shown that most of the research in this field is done quantitatively and little qualitative research has been done on the supportive activities for patients, nurses, and managers in the oncology ward during the COVID-19 pandemic. Since the phenomenon of support is related to human beings and human values, which have wide and complex dimensions, a comprehensive and in-depth study of human experiences of this phenomenon should be done through the qualitative method. In addition, Clarification of the experiences that the participants have encountered will lead to a better understanding of the phenomenon and help to develop appropriate support in the oncology ward. What is not known yet is what the supportive activities in the oncology ward are during the COVID-19 pandemic. Therefore, this study aimed to explore the supportive activities in the oncology ward during the COVID-19 pandemic.

Material and methods

This study was carried out in 2020 and 2021 using a conventional content analysis [16]. The research environment was oncology wards of hospitals located in Eastern and Southeastern Iran, namely the provinces of South Khorasan and Sistan & Baluchestan. The inclusion criteria were willingness to participate in the study, ability to communicate verbally and understand the Persian language. Nurses were included if they had at least two-year experience of working in the oncology ward. Cancer patients were recruited in the study if they had at least 4 to 6 months' history of treatment in that ward. The exclusion criterion was the participant's refusal to participate in the study. Participants were nurses, managers, and cancer patients in the oncology ward and they were selected by purposive sampling. To collect data, in-depth semi-structured face-to-face interviews were done. Interviews were continued until data saturation was achieved. Participants were informed about the objectives and the protocol of the research, as well as the interview method. The participants were assured that their participation was voluntary. After obtaining participants' written consent, the study was initiated. Interviews started with general questions. For example, nurses were asked: "What are your supportive activities experiences of caring for cancer patients during the COVID-19 pandemic?", patients were asked: "What support and care needs do you have in the oncology ward during the COVID-19 disease?" and managers were asked: "What are your supportive activities experiences in the oncology workplace during the outbreak of COVID-19?"

During the interviews, the researcher helped the participants to share their experiences without giving direction to the participants' activities. In addition, if necessary, the researcher used exploratory questions such as "Can you explain more?" or "What do you mean?". The date and place of the interviews were set according to the participants' wishes. The duration of each interview was 45 to 60 minutes for 1–2 times of sessions. The interviews were performed in 2020 and 2021. After recording the interviews on two recording devices, they were transcribed verbatim. In addition to individual interviews, field notes were also used for data collection. In this study, the data analysis process was carried out according to the steps proposed by Graneheim & Lundman [17]. The coding process was performed by researchers familiar with the coding process and analysis in the field of qualitative research. The unit of analysis in this study was the interview, and the semantic units were the sentences or paragraphs of the transcriptions. The concepts were extracted through transcribing the interviews verbatim and reading the transcriptions several times to get a general understanding of the supportive activities in the oncology ward. Each keyword or sentence was then given a code. In this stage, the first-level coding process was performed by labeling codes. In the next step, similar primary codes were grouped to form subcategories. Then, to increase homogeneity among the codes, categories were identi-

fied, and similar categories were merged. Finally, the main themes were extracted, and the degree of abstraction increased. After conducting 10 interviews with nurses, 5 interviews with managers, and 6 interviews with patients, data saturation was achieved. To manage the data, MAXQDA version 2020 was used. The rigor of the data was assessed using four criteria suggested by Lincoln at al. [17].

To verify the credibility of the study, the researchers collected the data for a long time, and the research findings were reviewed by participants and professors specializing in qualitative studies. To assure the transferability of the findings, participants with different demographic characteristics and experiences were recruited. To evaluate the dependability of the research findings, they were analyzed by another researcher, and her conclusions were compared with those of the main researcher. For confirmability, the findings of the research study were checked by other researchers. During data collection, the researcher tried to collect the data carefully and thoughtfully and avoid any kind of bias. In addition, wherever the researcher felt that she did not have sufficient and appropriate information about some of the participants' activities, she referred to those activities again during another interview to obtain more detailed information. In this study, ethical considerations, such as providing the necessary explanation for the participants, obtaining their written consent and permission to record their interviews, maintaining privacy and confidentiality of the participants' information, were observed in all stages. The right to withdraw from the study, respecting the participants' views and beliefs, equal attention and respect for all the participants, and not imposing the knowledge and beliefs of the researcher on the participants were also considered.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board (IRB) and the ethics committee of Birjand University of medical science (IR.BUMS.REC.1398.323). Oral and written consent was obtained from participants before data collection. Participants could leave the study at any time. Participants were assured that all their information would be confidential.

Results

The present study was performed with 21 participants (10 clinical oncology nurses, 5 managers, 4 oncology head nurses and 1 oncology hospital manager), and 6 cancer patients. In terms of gender, there were 3 male nurses, 7 female nurses, 4 female nurse managers, 1 male hospital manager, 2 female cancer patients, and 4 male cancer patients. The mean age of nurse participants was 31 years, managers were 44 years old, and patients were 50 years old. All patients and managers were married. Nine nurses were married and 2 were single. The level of education in all nurses was Bachelor of Science in Nursing (BSN). The concepts were extracted from the interviews based on the purpose of the study. Thus, these phrases, sentences, or paragraphs initially led to the formation of primary codes, 33 subcategories, and 9 categories. Then, by merging the categories, supportive activities in the oncology ward during the COVID-19 pandemic emerged in the form of three main themes, namely the perceive of threat supportive atmosphere in the oncology ward, Seeking support in the oncology ward, and supportive divergence. Categories and themes are listed in Table 1.

In this study, participants described their experiences of support in the oncology ward. The cancer patient's sense of desperation and need for support, the difficulty of working in the cancer ward, and close relationships governing the ward were the main categories extracted.

Table 1. Results extracted from the participants' experiences

Theme	Categories
Perceive of threat in supportive atmosphere in the oncology ward	Cancer patient's sense of desperation and need for support
	difficulty of working in the department
	Close relationships governing the department
Seeking support in the oncology ward	Professional support
	Patient Advocacy
Supportive divergence	Poor family support
	Poor perceived social support
	Unsupportive behaviors
	Distancing from supportive standards of working in an oncology department

Cancer patients' sense of desperation and need for support

Participants provided a variety of experiences regarding a cancer patient's feeling of desperation and the need for support during the COVID-19 pandemic. The incurable nature of the disease causes feeling desperate for the nurse, the emotional fragility of cancer patients, and the sensitivity and early suffering of cancer patients were recognized as subcategories of feeling desperate and need for support. These issues were expressed in the participants' experiences as follows:

"We get more upset when we see that our patient has an incurable disease and needs more support, It's very annoying that you have no hope of curing the disease …We understand them more than anyone else…" (Participant Manager, No.1).

"Well, we are very sensitive to some issues, we get upset quickly, we emotionally hurt very easily… This is due to our disease, and we are looking forward to receiving the necessary support…" (Participant cancer Patient, No. 3).

The difficulty of working in the oncology ward

According to the participants of this study, the difficulty of working in the oncology ward was due to the patients' disappointment with chemotherapy treatment outcomes and the high rate of death among young cancer patients, leading to a perceive of threat in supportive atmosphere in [the ward during the COVID-19 pandemic.

"It is unbearable for me to work in an environment where you have no hope for treatment of patients, with treatments that sometimes increase the suffering of the patient… COVID-19 disease has made the condition much more difficult…" (Participant Nurse, No. 4).

Close relationships governing the ward

From the participants' point of view, the relationships governing the ward were such that the patient had a friendly relationship with the nurse, patients were worried about each other, the nurse considers the patient as a member of her/his family, also a friendly relationship is formed between the nurses themselves and between the nurse and the physians.

"It is in such a way that we may call each other by the first name…since usually it is not a crowded ward. At night shift, for example, when we have more time, we come out of the room and talk to the nurses or when they come to our room to check our blood pressure, we ask questions and they answer. Our relationship is much closer…" (Participant cancer Patient, No. 6).

"In terms of relationship with colleagues, we are much more friendly here than in other hospital wards. We are very intimate, we go out together…" (Participant Nurse, No. 8).

Another theme extracted from the participants' experiences was the seeking support in the oncology ward during the COVID-19 pandemic. Which consisted of two categories, namely professional support and patient advocacy.

Professional support

This category comprises four subcategories, namely the manager's confidence and trust in subordinates, the oncology manager's efforts towards the retention of the workforce, understanding of oncology nurses and attention to their emotions, and increased motivation of the nurses through the manager's encouragement.

"Now, due to the COVID-19 disease and a lot of stress among colleagues… When I see that they are emotionally hurt, I give them time off to relax…" (Participant Manager, No. 1).

"In any case, it was very good that the manager herself had the experience and understood a nurse that was preparing the chemotherapy drugs for a few days. Somedays, she helped us and prepared the drugs when the ward was crowded. Anyway, this is an encouragement…" (Participant Nurse, No. 5).

Patient advocacy

This category consisted of subcategories of listening to the patients' concerns, the nurse as hope for cancer patients, gaining the trust of cancer patients, and empathizing with families of cancer patients.

"This relation is close and you cannot change it anymore. Because sometimes the patient really needs to talk with us, listen to her/his concerns, we really see that it works…, especially now that they go out less because of the COVID-19 pandemic, they are more emotionally fragile. For example, one day I went to the patient's room, and I saw that she is crying…I talked to her and comforted her…" (Participant Nurse, No. 6).

Another theme that emerged from the data was supportive divergence. This theme included categories of poor family support, perceived poor social support, unsupportive behaviors, and being far from supportive standards of caring in an oncology ward.

Poor family support

For this category, the nurse describes experiences in which he/she receives poor support in the life, with the nurse's spouse to insist change oncology ward. The nurse's family members being affected by her work in

the oncology ward. Influence on the nurse's own life was created by seeing the problems in the patients' lives, and the emergence and strengthening of hypochondrias feeling among oncology nurses and their families.

"My spouse is always telling me to change my ward. He says you have been here for a long time, and now you can change your ward, especially now that there is COVID-19, move to a new ward with less risk…" (Participant Nurse, No. 6).

"In the beginning when I start working, for example, I asked about patients' living conditions. Then, the patient tells me that his/her spouse left her/him after being diagnosed with cancer… I feel a lot of distress. I am pessimistic about everything about my husband and my life. I am overwhelmed with everything…" (Participant Nurse, No. 7).

"I did not think that caring for the patient would bother me like this. In the first week, I was very upset, I always thought that I had breast cancer. Then I did a test and mammography and made sure I had no problem… Now, when our patients have a drop in white blood cells, we do not know whether they have the COVID-19 disease or it is due to their chemotherapy drugs… We all have the feeling of being infected with the COVID-19 disease…" (Participant Nurse, No. 2).

Poor perceived social support in the oncology ward

Participants in this study described various experiences in this regard, such as friends and acquaintances' negative perception of working in the oncology ward, having a negative view of those working in the chemotherapy ward, and the unwillingness of nurses in other ward to move to the oncology ward.

"I am often asked: where do you work? And when I say in the chemotherapy ward, they feel apprehension and ask again how you can work there? Other people feel stress about working in such environments. Or, for example, my friends who are in other hospitals ask how you can work there. They make a mountain out of working in the oncology ward and caring for cancer patients… These days, they fear of the COVID-19 disease and tell me to change my ward, it is difficult working there…" (Participant Nurse, No. 7).

"One issue is that if I want to change my ward, others have a negative attitude towards us, toward these wards. For example, if they understand I work in the oncology ward, they ask me isn't it difficult? Aren't you depressed? Don't you hurt emotionally? Others have such ideas if I want to change my ward. Other nurses don't accept to change their ward with me, They have a negative view. Recently, no new nurse have come to our ward. Other hospital staffs also have a negative view of us…" (Participant Nurse, No. 5).

Unsupportive behaviors

These behaviors included his/her superiors did not understand, challenges in professional communication, and attempts to leave the ward due to conflict with the manager. The nurse's compassion was annoying to the patient and the relationship between the head nurse and the nurse and the physician was challenging.

"This head nurse also adds a shift to nurses. For example, she calls us and without asking our opinion gives us an additional shift. These behaviors lead to tension between me and my colleagues… because all of us are stressed out due to fear of developing the COVID-19 disease but they again give us additional shifts. They don't understand us." (Participant Nurse, No. 5).

Distancing from supportive work standards in the oncology workplace

"There are a lot of tensions between us… I think unfortunately the nurses have not supported each other since our previous manager left…" (Participant Nurse, No. 5).

Being far from supportive care standards in the oncology ward we found in this concept the lack of adequate protective equipment to care for cancer patients, lack of clear standard of care for working in the oncology ward, and insufficient allocation of time off, the need for higher salaries and benefits for oncology nurses.

"We do not have a clean room to prepare the chemotherapy drugs. We do not have special facilities. We only wear a filtered mask. They should care for the health of nurses and provide a clean room. This is the standard. At the beginning of the outbreak of the COVID-19 diseases, they gave us personal protective equipment such as gowns and aprons, but after a while, they say we cannot provide these…" (Participant Nurse, No. 5).

"It even seems that they can use psychologists in the chemotherapy ward… A psychologist is needed. It makes no difference, both the patient and the nurse need counseling. The psychologist can teach us how to behave with the patients and their companions, they can hold training classes for patient companions… During the outbreak of the COVID-19 disease, this need is felt more. All of us, the patient, his/her family, and the nurse, suffer from mental health problems…"(Participant Nurse, No. 5).

"There is no difference between nurses in terms of financial issues, time off, and benefits… They paid us little for working during the outbreak of the COVID-19 disease." (Participant Nurse, No. 4).

"I believe we should even give force time off to nurses working in this ward, but unfortunately, again due to work problems and shortage of nurses, some days, they have to work two shifts for two shifts even

and without rest. These days, our nurses are constantly tested positive for the COVID-19 disease and they do not come to work and other nurses have to cover their shifts…" (Participant Manager, No.2).

Discussion

The purpose of this study was to explain the supportive activities in the oncology ward during the COVID-19 pandemic. The first extracted theme was the supportive atmosphere in the oncology ward. In line with the present study, Maningo-Salinas [9] has concluded that the oncology nursing environment is a challenging setting due to the physical and psychological stress that cancer patients face. According to Slatyer et al. [19] a supportive and encouraging work environment increases motivation.

Other studies have shown that some features of the hospital can create a positive work environment, increase nurses' job satisfaction, and support their efforts in providing quality care to patients [20].

According to the experiences gained from this study, patient support was one of the factors that created a supportive atmosphere in the oncology ward during the COVID-19 pandemic. Similarly, Evans Webb et al. [5] have considered support as the main need of cancer patients. Soltani and Khoshnood [6] also have stated that patient support helps cancer patients cope with the stress of the disease and cancer treatment. The emotional fragility and early suffering of cancer patients was another experience highlighting the nature of their support-seeking behavior during the COVID-19 pandemic. As in the study by Korotkin et al. [21], we found out that patient's vulnerability makes patient support necessary in nursing. This vulnerability has increased during the COVID-19 disease.

Seeking support in the oncology ward was the second theme extracted in this study. This theme comprises two categories, namely professional support and patient advocacy. Similarly, Sodeify and Habibpour [22] have reported that several factors affect the nurse's support, one of which is the managerial factor.

Regarding the manager's trust, Toh et al. [13] have also stated that nursing managers can provide a suitable work environment through increasing organizational support. Managerial characteristics as well as the amount of support that nurses receive for the provision of care affect their performance [24]. Martinussen and Davidsen [14] also have reported that managers' support for nursing staff could play a key role in their productivity. Tomey [25] also emphasizes the need for nursing managers' support and reports that their support empowers employees and improves their efficiency. He believes that supporting nurses prevents unnecessary pressure on them and motivates nurses to provide the best support and care to their patients. Therefore, considering that the nursing staff are very tired due to the outbreak of the COVID-19 disease, they also need psychological support. It seems that the best measure for supporting nurses is the attention and encouragement of managers.

The third theme found in this study was supportive divergence, which included categories of poor family support, poor perceived social support, unsupportive behaviors, and being far from supportive care standards in the oncology ward. A noteworthy point in the participants' experiences regarding this category was that nurses's family members_were distressed due to working in the oncology ward. In this regard, Buonocore and Russo [25] also believe that nurses tolerate more work-family conflict due to working in unusual conditions, insomnia, and insomnia-related problems, being in contact with patients and observing painful situations. Concerning the results about leaving the oncology ward. Ekici et al. [26] have also stated that work-family conflict is associated with the oncology nurses. In particular, the higher the level of conflict, the higher the leaving rates will be. Consistent with the results of the present study, Fathi et al [27] state that the increased conflict with family, spouses, and children in nurses was associated with the COVID-19 disease. Another experience of the study participants was the lack of perceived social support for working in the oncology ward. Fathi et al. [27] also reveal that staying away from others due to fear of transmuting or getting the COVID-19 disease was one of the experiences of medical staff leading to a lack of social support. The other experience revealed in this study was unsupportive behaviors during the COVID-19 pandemic. These behaviors in nurses included not being understood by the managers, challenging professional communication, making attempts to leave the oncology ward due to having conflict with the manager, and challenging communication between the head nurse, nurse, and physician. Similar to the present study, Wazqar [28] shows that unsupportive management is a kind of despotic and violent supervision over subordinates. In other words, the manager behaves in a way that shows a lack of interest in subordinates, a lack of respect for them, and incomprehension of their personality. The managers' support plays an important role in the motivation, and self-efficacy of employees. Regarding being far from the supportive standards in oncology care , we found staff's lack of time off and low salaries and benefits for nurses working in the oncology ward. Wong at al. [29] also concludes that nurses experience many problems due to long working hours, irregular work schedules, limited weekends, excessive job demands, and insufficient earnings. Another experience in this study was

the lack of personal protective facilities. Also Sperling [30] identified personal protection as one of the main concerns of nurses during the outbreak of the COVID-19. They believed that a nurse should be assured first about the provision of personal protection equipment to provide quality care.

Limitations

In this qualitative study, the participants were selected from a diverse background, but these findings may not be representative for the experiences of all the nursing and managers and patients. Since this study was conducted during the COVID-19 epidemic, it was very difficult to reach the participants and arrange interviews with them.

Conclusions

The results of the present study showed that one of the important aspects of cancer management is the provision of supportive care. Awareness about these issues can play an important role in the oncology ward to provide effective supportive care for cancer care during the COVID-19 pandemic. Also the results of the study have shown that the supportive activities in the oncology ward during the COVID-19 pandemic are affected by various factors. The experiences of participants provide new insight into supportive activities around managing oncology wards supportive needs during such stressful times.

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Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Factors affecting change in renal function after contrast-enhanced computed tomography in cancer patients

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ABSTRACT

Objectives. Contrast-enhanced computed tomography (CECT) is the most common form of assessing the effectiveness of cancer patient treatment. However, an injection of an iodine-based contrast agent can cause acute kidney damage (AKI). To determine the frequency and factors affecting post-contrast kidney function deterioration during oncological treatment.

Material and methods. Kidney function in cancer patients with solid tumors undergoing a total of 206 CECTs was retrospectively analyzed.

Results. Two hundred and six CECT procedures in 79 patients (age 68.4 ± 10.6 years) were included in the study. The median eGFR before CECT according to the MDRD was 81 mL/min/1.73 m^2 (IQR 26). The median time between CECT and kidney function examination was 8 (IQR 8) days. In the whole group, the median eGFR change defined as the difference between eGFR after and before CECT was 0.0 (9.0) mL/min/1.73 m^2 and was not significant. eGFR decreased in 100/206 (48.5%) CECT procedures with the median difference = –5.0 (6.0) mL/min/1.73 m^2. However, clinically significant deterioration of renal function (an increase in SCr of > 0.3 mg/dL) was found only in two cases (0.9%). The change in eGFR associated with CECT correlated significantly ($p < 0.05$) with initial creatinine ($r = 0.117$) and urea ($r = 0.158$), but not with age and comorbidities. After dividing the analyzed population according to the median GFR, it turned out that in the group of patients with eGFR < 81 mL/min/1.73 m^2, the median difference in GFR level was 1 (IQR 10), and in the group with a higher eGFR level the median was –1 (IQR 8.5), which was statistically significant ($p = 0.03$). The multivariate logistic regression analysis in subsequent reduced models confirmed that SCr, uric acid level, and the use of antimetabolites were the factors independently reducing the risk of deterioration of renal function after CECT.

Conclusions. CECT can be responsible for kidney function deterioration; however, it has no impact on oncological treatment.

Key words: contrast-enhanced computed tomography, CECT, post-contrast kidney function, cancer, oncological treatment

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Introduction

Cancer treatment in advanced stages of the disease can prolong survival; however, it is connected with toxic side effects. The basic form of monitoring response to anticancer treatments is contrast-enhanced computed tomography (CECT); however, administration of iodinated contrast media (CM) can be complicated by a decrease in renal function. The kidney function deterioration is usually mild, and renal function usually

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returns to baseline values within 3 weeks; unfortunately, post-contrast acute kidney injury (PC-AKI) is responsible for increased short- and long-term morbidity and mortality [1]. It is estimated that up to 2% of all CECT examinations are connected with acute kidney injury (AKI), and administration of iodinated CM can be responsible for almost 11% of all cases of AKI [2]. However, recent meta-analyses showed PC-AKI incidences of 5–6.4%, and in 1% of all patients, kidney function deterioration persisted for 2 months [3, 4]. AKI and chronic kidney disease are common in cancer patients [5–9].

This study aimed to assess real risk of kidney function deterioration in cancer patients treated at the Oncology Department after iodinated CECT measuring the serum creatinine (SCr) and the estimated glomerular filtration rate (eGFR). The data collected in this study allowed for evaluation if CECT gives clinically significant renal function deterioration and contributes to interruptions in oncology treatment.

Materials and methods

Study design

This was a single-center retrospective analysis of all consecutive patients who were treated at the Oncology Department at the Medical University of Warsaw from October 2020 to January 2021. If the patient started the treatment before October 2020, the data about earlier CECT scans were also included. Data were collected on designed proformas by the study team.

Study population

We included adult patients (≥ 18 years) with active solid tumors who underwent CECT. All patients have SCr and eGFR measured according to modification of diet in renal disease (MDRD) before the CT scan and in subsequent follow-up. CECT were performed between chemotherapy (CHTH) courses, usually a few days after a CHTH administration. Patient demographics, underlying cancer diagnoses, medical conditions, concurrent nephrotoxic medication, and laboratory variables were obtained. Available follow-up creatinine results were collected for the next chemotherapeutic course after CECT. The primary endpoint of this study was the frequency of post-contrast kidney function deterioration during oncological treatment defined by an absolute increase of SCr to at least 0.3 mg/dL or at least a 1.5-fold increase over baseline SCr.

Statistical analysis of the results was performed using the Statistica software (StatSoft Inc.), version 12.

Results

A total of 206 CECT examinations in 78 oncology patients with a solid tumor were retrospectively identified by a database search (Tab. 1). Medications that were received by the patients are presented in Table 2.

Table 1. General characteristics of patients in the study (n = 78)

Variable	Value	Percentage (%)
Age (years)		
Mean	67.6 (32–89)	–
Median	68	–
≥ 70	34	–
70–60	28	–
<60	16	
Sex		
Male	43	55
Female	35	45
Mean eGFR before IV contrast (mL/min)	80.53	
Comorbidities		
Yes	56	72
No	22	28
Diabetes		
Yes	26	33.3
No	44	56.7
Hypertension		
Yes	51	65.4
No	27	34.6
Heart disease		
Yes	16	20.5
No	62	79.5
Hemoglobin ≤ 9.5 g/dL		
Yes	11	14
No	67	86
Tumor type		
Digestive tract cancer	31	40
Pancreatic cancer	15	19
Cholangiocarcinoma	8	10
Liver cancer	7	9
Other	17	22
Chemotherapy		
No	10	13
Yes	68	87

IC — intravenous contrast; eGFR — estimated glomerular filtration rate

The median eGFR according to the MDRD was 81 mL/min/1.73 m^2 (IQR 26). The median time between CECT and kidney function examination was 8 (IQR 8) days. An increase (SCr > 0.3 mg/dL) was found in two cases (0.9%). There was no statistically significant difference in the SCr and eGFR before and after CECT [0.875 (0.250) *vs.* 8.70 (0.260) mg/dL; p = 0.962 and 80.0 (26.0) *vs.* 81.0 (27.0) mL/min/1.73 m^2; p = 0.851]. However, after dividing the analyzed population according to the median eGFR, it turned out that in the group of patients with initial eGFR < 81 mL/min/1.73 m^2, mean GFR rose after CECT [the median eGFR difference = 1 (IQR 10) mL/min/1.73 m^2], but in the group with a higher initial eGFR, the median eGFR decreased after CECT [median difference = –1 (IQR 8.5) mL/min/1.73 m^2], which was statistically significant (p = 0.03) However, it was not clinically substantial as it had no impact on chemotherapy administration. A statistically significant negative correlation was found between the baseline eGFR value and the eGFR difference before and after CECT (r= –0.143; p < 0.05) and between baseline Scr and urea and the eGFR difference before and after CECT (respectively r = 0.171 and r = 0.158; p < 0.05). No correlation was found between the CECT number or comorbidity and the eGFR difference.

The univariate logistic regression analysis is presented in Table 3. The multivariate logistic regression analysis in subsequent reduced models confirmed that SCr, uric acid level, and the use of antimetabolites were the factors independently reducing the risk of deterioration of renal function after CECT (Tab. 4).

Table 2. Administered drugs

Medication	Number	Percentage (%)
Chemotherapy	69	
Platin compound	13	32
Antimetabolite*	38	55
TKI	6	8
Monoclonal antibodies	9	13
Others chemotherapeutic agents	23	33
Nephrotoxic drugs	36	
Zoledronic acid	6	17
NSAID	6	17
Diuretics	8	22
ACI/ARB	28	77

*Antimetabolite = gemcitabine, capecitabine, 5-fluorouracil; TKI — tyrosine-kinase inhibitors; NSAID — non-steroidal anti-inflammatory drug; ACI/ARB — angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers

Discussion

Cancer patients are in the high-risk group for kidney injury, and its consequences and the frequency of AKI was highest in patients with renal cell cancer, liver cancer, pancreatic cancer, and hematological malignancies [5, 6]. Clinicians are afraid of kidney injury connected with iodinated CM, make an effort to avoid additional risk factors, and try to assess the effectiveness

Table 3. Univariate analyses of variables for possible association with estimated glomerular filtration rate deterioration

Variable	OR	95% CI	p
SCr before CECT	0.163	0.038–0.693	0.0140
Uric acid before CECT	0.590	0.361–0.963	0.0349
CHTH	0.367	0.169–0.796	0.0111
Platin compound	0.453	0.223–0.923	0.0293
Antimetabolite*	0.450	0.254–0.796	0.0061
TKI	1.571	0.574–4.302	0.3791
Monoclonal antibodies	0.490	0.235–1.022	0.0572
Bisphosphonates	2.490	0.908–6.832	0.0764
ACE-I	1.091	0.610–1.950	0.7691
Diuretics	0.751	0,289–1.951	0.5566
NSAID	1.571	0.574–4.302	0.3791
Three concomitant nephrotoxic drugs	1.061	0.065–17.189	0.9670
Hemoglobin level	0.941	0.809–1.094	0.4301

*Antimetabolite = gemcitabine, capecitabine, 5-fluorouracil; SCr — serum creatinine; CECT — contrast-enhancement computed tomography; CHTH — chemotherapy; OR — odds ratio; CI — confidence interval; TKI — tyrosine-kinase inhibitors; ACE-I — angiotensin-converting-enzyme inhibitors; NSAID — non-steroidal anti-inflammatory drug

Table 4. Subsequent reduced multivariate logistic regression models, with factors independently reducing the risk of worsening renal function after contrast-enhancement computed tomography

Variables	Model 1	Model 2	Model 3
	CHTH	CHTH	CHTH
	Platin compound	Platin compound	Platin compound
	Antimetabolite*	Antimetabolite*	Antimetabolite*
	Uric acid before CECT	Uric acid before CECT	
	SCr before CECT		
Results	**SCr before CECT**	**Uric acid before CECT**	**Antimetabolite***
OR ± 95% CI	0.0003 (0.0000–0.0933)	0.590 (0.361–0.963)	0.45 (0.254–0.796)
Significance — p	0.005	0.035	p = 0.006

*Antimetabolite = gemcitabine, capecitabine, 5-fluorouracil; SCr — serum creatinine; CHTH — chemotherapy; CECT — contrast-enhancement computed tomography; OR — odds ratio; CI — confidence interval

of CT treatment without contrast administration or by ultrasonography. This strategy does not allow for an accurate assessment of the effectiveness of the treatment and thus unnecessarily exposes the patient to suboptimal treatment because, in our study, clinically relevant deterioration in renal function after administration of iodinated contrast in cancer patients was detected in 0.9% of analyzed cases. The frequency in our study is lower than in previous studies [2]. Moreover, the performed analyzes allow us to state that the short interval between the administration of chemotherapy and CECT did not result in the deterioration of kidney function, even though such a relationship has been reported [7, 8]. Similarly, oncological treatment, use of other potentially nephrotoxic drugs, age, and comorbidities were not connected with the risk of renal injury. Moreover, in the examined population, patients during active oncological treatment (mainly patients that received antimetabolites) were in the group with a lower risk of eGFR deterioration after CECT than patients during follow-up or patients before the start of the therapy. It seems that this association is connected with ensuring adequate hydration as part of premedication; however, more research is needed in this area.

In the analyzed population, the median difference in GFR level after CECT was 1 in the group of patients with eGFR < 81mL/min/1.73 m^2 which means that in this group, CM administration was connected with kidney function improvement. Similarly, patients with higher SCr or higher urea levels have a lower risk of worsening renal function after CECT. This phenomenon occurs in patients with lowered eGFR values in which the ability to remove excessive amounts of water from the body is impaired because of CKD (chronic kidney disease). It could be connected with higher hydratation before examination compared to a cohort of patients with normal eGFR values due to stop diuretics taking 48 h before ICM administration. Proper hydration enables a reduction in the tubular concentration of ICM and its viscosity, a less marked stimulation of the renin-angiotensin-aldosterone system, inhibition of antidiuretic hormone synthesis, and minimization of the reduction of nitric oxide (NO) and prostacyclin synthesis [8]. Each patient before ICM administration had an intravenous fluid infusion or is pretreated by oral water intake. Oral water intake, by suppressing vasopressin release, leads to a rapid increase in diuresis and provides rapid short-term renal protection. Conversely, the renal response to intravenous administration of isotonic saline is delayed — as saline loading suppresses the renin-angiotensin-aldosterone system — but offers long-lasting renal protection [2].

As a result of a higher amount of water in the body than in healthy individuals, in those patients, the osmolality and cytotoxicity properties of ICM decrease. Additionally, the serum creatine concentration decreases, and as a consequence, eGFR value calculated within CKD-EPI equilibrium could be greater than in the case of less hydrated patients.

According to previous reports one of the most significant risk factors for AKI is pre-existing CKD [9], and in our population, eGFR < 60 mL/min/m^2 was detected only in 32 cases (15.4%). Patients with kidney, liver, and pancreatic cancers, which are also connected with a high risk of AKI, constituted only 36.7% of our study population. We assessed kidney function within a few days after CECT so it cannot be ruled out that the frequency of deterioration of renal function after CECT could be higher if the control test was performed earlier. It should also not be forgotten that kidney injury can be caused by many reasons, including fluid restriction or taking non-steroidal anti-inflammatory drug (NSAID), so the deterioration in renal function observed in these cases may be related to CM administration only temporarily. However, the low percentage of patients with a significant increase in SCr allows us to conclude that the possible CECT-related kidney injury was not clinically significant, as the renal function spontane-

ously returned to the baseline. Besides, AKI did not affect the oncological treatment, was not a reason for treatment interruption or dose reduction and was not associated with increased toxicity.

Our study has some limitations. It is retrospective in character, and there is no comparison with different contrast agent volumes or concentrations. Besides, due to the retrospective character of the study, not all potential coexisting pathologies could be excluded as direct causes of kidney function deterioration. However, we found a relatively low incidence of PC-AKI during oncological treatment. In addition, there was no statistically significant difference in SCr before and after CECT. Hence, the use of the contrast medium seems to be safe in oncology patients.

Conclusions

In patients with cancer kidney function deterioration is common and it causes interruptions in therapy and decrease the treatment effectiveness. One of the possible reasons for this is CECT. However, clinically significant kidney injury was detected in 0.9% of analyzed cases which is relatively lower as compared to previous studies done on cancer patients. Moreover, the interval between the administration of chemotherapy and CECT did not influence on kidney function. Besides, the identified disorder had no influence on the oncological treatment - it was not a reason for treatment interruption, dose reduction and was not associated with an increase in toxicity so we can conclude that the use of the contrast medium is safe in oncology patients.

Conflict of interest

Authors declare no conflict of interest.

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ORIGINAL ARTICLE

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Diagnostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography over conventional imaging studies to detect malignant lesions in staging and restaging after radically treated primary and recurrent locoregional cutaneous melanoma

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ABSTRACT

Introduction. Cutaneous melanoma (CM) has a high metastasizing potential and requires many imaging tests for accurate staging and restaging. As a hybrid imaging method, 18F-FDG PET/CT has the power to diagnose clinically undetected regional and distant metastatic disease with a better detection rate than conventional imaging. The aim of our study was to assess the value of 18F-FDG PET/CT in detecting different types of malignant lesions – local recurrences, regional lymph nodes (RLN), in-transit (ITM) and distant metastases (DM) after radical excision of the primary lesion or regional recurrence.

Materials and methods. A retrospective analysis was performed of all patients with CM referred for 18F-FDG PET/CT for staging or after resection of locoregional recurrent disease. All patients had a combination of pre-PET/CT conventional imaging studies (CIS), including a whole body computed tomography (CT) and ultrasonography (US) of the RLN basin/s. The results from 18F-FDG PET/CT were compared with the CIS results.

Results. 246 consecutive patients, aged 10–87 years were included with identification of 71 malignant lymph nodes, 4 local recurrences, 28 ITM, and 65 DM in total. The detection rate of 18F-FDG PET/CT for RLN was 84.5%, and in the diagnosis of ITM and DM, it reached a sensitivity of 100.0% with 0.7% of false positive results.

Conclusions. 18F-FDG PET/CT has an invaluable role in the detection of small, clinically silent ITM and DM and has a smaller value in RLN detection. It may guide the process of selection of suspicious lesions, suitable for biopsy or further ultrasound follow-up.

Key words: 18F-FDG PET/CT, melanoma, staging, restaging

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Introduction

Cutaneous melanoma (CM) is the fifth most common cancer in men and women [1, 2], with a worldwide incidence in 2020 of 3.8% in males and 3.0% in females. It remains the predominant cause of skin cancer death. [3] CM is an aggressive malignant disease with a very high risk for recurrence and dissemination.

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Around 84% of cases present with localized disease, 9% with involvement of regional lymph nodes, and 4% with distant metastases (DM) at diagnosis [1]. Adequate staging and restaging after initial management of recurrent disease are crucial for early radical treatment or appropriate subsequent therapy of clinically silent disease, unrecognized by conventional imaging studies (CIS). Sentinel lymph node biopsy (SLNB) is the acknowledged gold standard for pathological staging of clinically negative lymph nodes. Ultrasound is the most important noninvasive method for regional lymph node staging and follow-up. The role of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) is predominantly in whole-body staging in advanced stages (III and IV) and restaging after CM progression.

Aim

To assess the diagnostic value of 18F-FDG PET/CT for detection of different types of malignant lesions in patients with CM — regional lymph nodes, *in-transit*, distant metastases, and local recurrences after radical excision of the primary lesion, or radical treatment of the local recurrent disease, in comparison with CIS. The latter included contrast-enhanced computed tomography (CECT) of the thorax, abdomen, pelvis, and ultrasonography (US) of regional lymph nodes.

Material and methods

Patients and inclusion criteria

A retrospective analysis was performed of all CM patients without DM disease, referred for staging and restaging after radical surgical treatment between January 2007 and December 2018. We identified 246 consecutive patients with those inclusion criteria: 103 (41.9%) female and 143 (58.1%) male, aged 10–87 years, mean of 59.19 years (SD 13.35). The mean Breslow thickness of the primary lesions was 4.63 mm (SD 2.85 mm), ranging from 0.75 mm to 17.0 mm. All of them underwent 18F-FDG PET/CT at the Nuclear Medicine Department of St Marina University Hospital, Varna. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics

Characteristics	n (%)
Stage	
IIA	31 (12.6%)
IIB	51 (20.7%)
IIC	48 (19.5%)
IIIB	18 (7.3%)
IIIC	79 (32.1%)
IIID	19 (7.7%)
Localization	
Upper Extremity	25 (10.2%)
Lower Extremity	59 (24.0%)
Trunk	119 (48.4%)
Head & Neck	38 (15.5%)
Regressed, T0	7 (2.8%)
Indication	
Staging	141 (57.3%)
Restaging after radically treated regional recurrent disease	105 (42.7%)

Method

The examinations were held with Gemini TF PET/CT, Philips, equipped with 16-slice CT. The PET/CT scan was performed at 60–90 min intervals after 18F-FDG application. A whole-body scan was performed for all patients, including the region of excision. At the time of 18F-FDG administration, fasting plasma glucose values were lower than 150 mg/dL in all patients. If the primary CM was located in the upper extremity, the contralateral arm was used for ^{18}FDG administration.

SLNB was performed in 28 of all 141 patients, referred for staging with 18F-FDG PET/CT. SLNB was performed by a combination of radionuclide scintigraphy and gamma probe-guided surgery and injection of patent blue V.

18F-FDG PET/CT was a staging method in patients with CM in the IIA-IIID stage. In patients for restaging after radical excision of the recurrence, we assessed the first 18F-FDG PET/CT scan. Patients with initial DM at diagnosis, second primary and metachronous tumors were excluded. All the patients had a pre-18F--FDG PET/CT, diagnostic CT of the thorax, abdomen, and pelvis and ultrasonography of the regional lymph node basin/s. To avoid false positive results, staging and restaging were performed one month after tumor or lymph node excision or two weeks after a biopsy.

We explored the ability of 18F-FDG PET/CT to reveal different types of malignant lesions, including local recurrence, regional nodal involvement, *in-transit* (ITM), and distant metastases (DM), performing lesion-by-lesion analysis in patients with CM. In every patient we studied the diagnostic value of 18F-FDG PET/CT vs. a combination of CIS, identifying four categories of malignant lesions: local recurrence, regional lymph nodes, ITM, and DM. We assessed the true positive, true negative, false positive, and false nega-

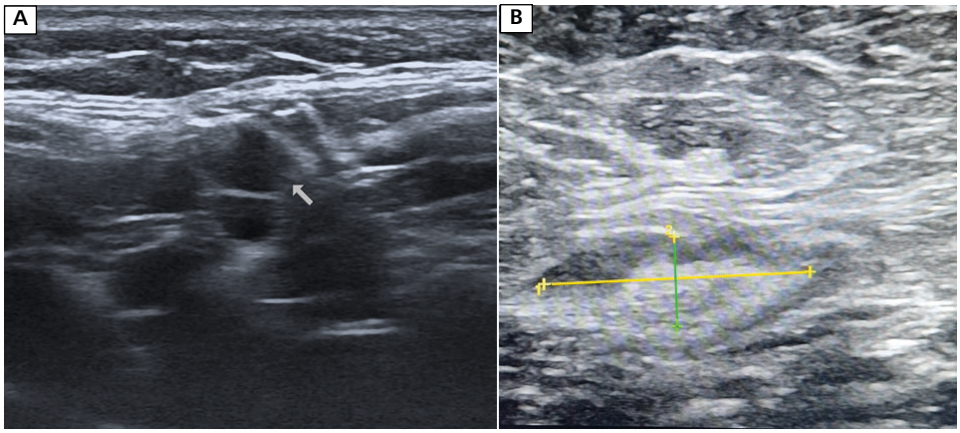

Figure 1. Suspicious sentinel lymph nodes with oval or rounded shape, local thickening of the cortex, and dislocated gate; **A.** Inguinal lymph nodes; **B.** An axillary lymph node

tive results in staging and restaging after progression. The advantages and weaknesses of the method in all of the above lesions, in comparison with CIS, were studied in detail. The role of 18F-FDG PET/CT in patients after SLNB was also studied. We also explored the additional value of 18F-FDG PET/CT in patients after SLNB.

Image interpretation

Cutaneous melanoma lesions are characterized by high 18F-FDG avidity. This is the reason why 18F-FDG PET/CT has a very good sensitivity even in subcentimeter lesions. The image interpretation always included CT and PET-image interpretation, separately and in fused images. Special attention was paid to regional lymph node interpretation, with the nodes divided into three categories – definitely malignant, non-malignant, and suspected of malignancy. Suspicious lymph nodes were those with at least two of the following characteristics: a round shape, partly or completely missing fatty hilum, and FDG uptake close to that of the liver. All of them were considered PET-negative, but a follow-up study was recommended.

Pathological confirmation of suspicious/positive lesions with FDG uptake on PET/CT was pursued. If pathological confirmation was not possible, clinical outcome and imaging after 6 months were used as gold standards. Scans were classified as true-positive if metastatic melanoma was suggested and confirmed and as false-positive if the suspected metastatic melanoma was confirmed to be something else. Scans that were considered negative were classified as true-negative if the patient did not develop a recurrence during the 6 months following the baseline imaging. Scans were considered false-negative if the baseline scan failed to reveal the initial suspected metastatic lesion that was still present or if evidence of any further metastasis was established during the 6 months of follow-up.

Ultrasonographic characteristics of malignant lymph nodes

The RLN assessment was made in oncological centers as part of the conventional staging of CM patients. We compared the 18F-FDG PET/CT study results with ultrasonographic files in patient documentation. The main features of malignant lymph nodes are round shape, loss of echogenic fatty hilum, cystic change, calcification, and abnormal peripheral vascularity (Fig. 1).

Sentinel lymph biopsy technique

Twenty-eight of the patients referred for an 18F-FDG PET/CT scan staging had previously performed a sentinel lymph node biopsy procedure. It included 1) injecting 0.28 to 10μCi of a radiopharmaceutical agent (99Tcsulphur colloid) at 4 intradermal spots around the biopsy scar of the MM, 2) examining the patients in a gamma camera to make a lymphoscintigraphic map, 3) visualizing the regional lymph drainage, location and number of sentinel lymph nodes, and 4) presence or absence of in-transit lesions in the operating room. One ml of lymphotropic dye (Patent Blue V) was intradermally applied at ten locations around the scar. After 6 to 10 minutes, the areas marked on the lymphoscintigraphic map were explored to find the sentinel lymph node. The blue node and its location corresponded to the spot as indicated on the map.

Ethical considerations

All of the patients included in the study signed informed consent allowing us to use the results of their imaging studies in scientific projects while maintaining rules of confidentiality. This retrospective study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committee at the Medical University "Prof. Paraskev Stoyanov", Varna, Bulgaria.

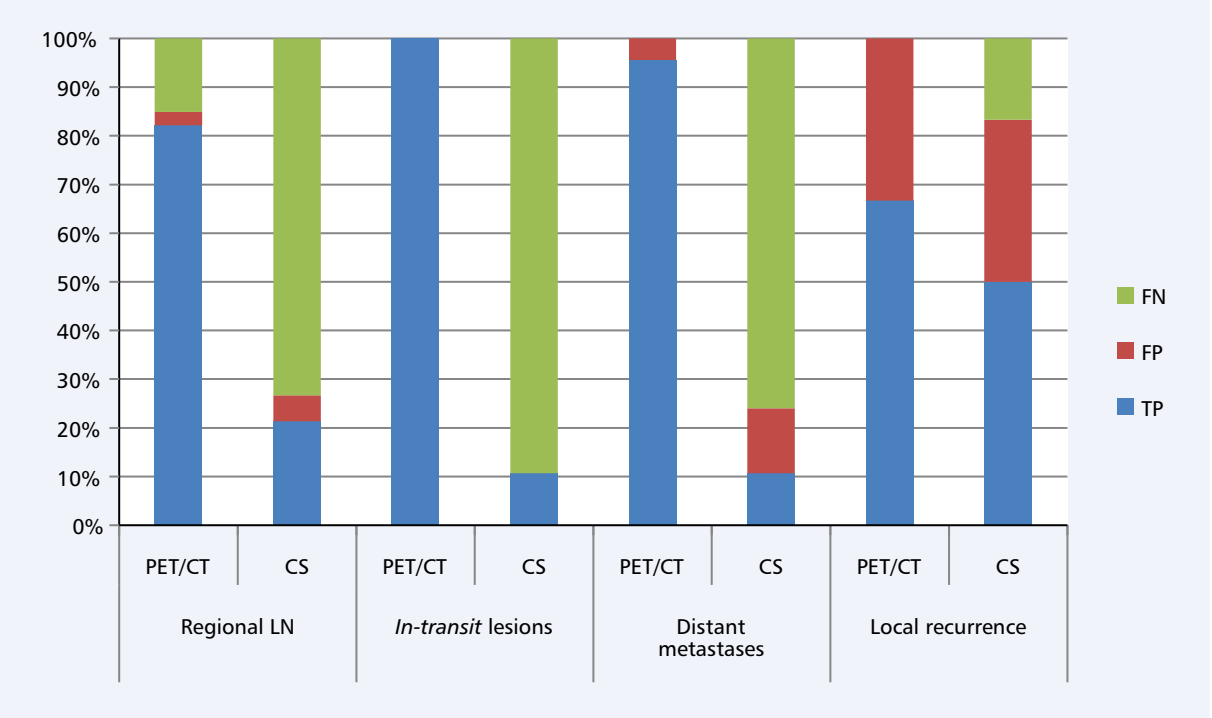

Figure 2. Diagnostic accuracy of 18F-FDG PET/CT in different malignant lesions in cutaneous melanoma patients; PET/CT — positron emission tomography/computed tomography; CS — conventional studies; LN — lymph node; FN — false negative; FP — false positive; TP — true positive

Statistics

The statistical analysis was done using IBM®SPSS®Statistics, v.19.0.0. The tables were made with Microsoft Office 2010. We processed the qualitative data of the patients using descriptive statistics. The quantitative data were presented as mean values, ranges, and standard deviations of the variables. The accuracy of 18F-FDG PET/CT was studied by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the accuracy of 18F-FDG PET/CT in comparison with a combination of CIS, using lesion-based analysis.

Results

In total, in all patients, there were 71 malignant lymph nodes, 4 local recurrences, 28 cases of ITM, and 65 DM, confirmed histologically or during follow-up. 18F-FDG PET/CT identified 84.5% of all malignant lymph nodes (60/71), all local recurrences, ITM, and DM. 18F-FDG PET/CT additionally identified 12 undiagnosed DMs in patients with an initial non-metastatic result from conventional imaging (Fig. 2).

The true positivity rate of conventional studies in the detection of malignant lymph nodes was significantly lower than that of 18F-FDG PET/CT, leading to identification of only 16 (22.5%) true positive lymph nodes out of the 71 metastatic lymph nodes (Tab. 2, 3).

18F-FDG PET/CT had 100% sensitivity in the diagnosis of ITM, revealing all of them (28/28). By contrast, CIS performed worse in those lesions with a sensitivity of 10.7% (3/28) (Tab. 2, 3).

In our study, only 28 of all 141 patients, referred for staging with 18F-FDG PET/CT, had previous SLNB. In 12 (42.9%) of them, 18F-FDG PET/CT detected additional lesions, which changed the stage and further management of the patients. In 3 of the patients with positive SLN (stage III), additional regional lymph nodes were found, in 2 — ITM and in 6 — previously undetected DM. In one patient in the IIA CM stage and with negative SLNB, one ITM was detected. CIS performed significantly poorer, also in detecting ITM, as only 3/28 (10.7%) of them were detected (Tab. 4).

18F-FDG PET/CT has a 100% detection rate of DM and revealed all 65 lesions. Most DM were missed by CIS — 57/65 (87.7%), mainly because of small size but also due to hard-to-diagnose metastatic sites, such as peritoneal or bone marrow lesions.

In the small group of 4 patients with the local recurrent disease only, there was no significant difference in the detection rate between 18F-FDG PET/CT and CIS, mostly because of false positive lesions after excision (Fig. 3, 4).

Table 2. Diagnostic accuracy of 18F-FDG PET/CT in different cutaneous melanoma lesions

Metastatic localizations	Diagnostic accuracy of 18F-FDG PET/CT				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Regional LN	84.50	98.90	96.80	94.00	94.70
In-transit lesions	100.00	100.00	100.00	100.00	100.00
Distant metastases	100.00	98.30	95.60	100.00	98.80
Local recurrence	100.00	99.20	66.70	100.00	99.20

PPV — positive predictive value; NPV — negative predictive value; LN — lymph node

Table 3. Diagnostic accuracy of conventional studies in different cutaneous melanoma lesions

Metastatic localizations	Diagnostic accuracy of conventional imaging methods				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Regional LN	22.50	97.70	80.00	75.70	76.00
In-transit lesions	10.70	100.00	100.00	89.70	89.80
Distant metastases	12.30	94.50	44.40	75.00	72.80
Local recurrence	75.00	99.20	60.00	99.60	98.80

PPV — positive predictive value; NPV — negative predictive value; LN — lymph node

Table 4. 18F-FDG PET/CT findings in patients who had sentinel lymph node biopsy (SLNB) performed before imaging.

Additional 18F-FDG PET/CT findings	SLNB result	
	positive	negative
Regional lymph node	3	0
Distant metastasis	6	0
In-transit metastasis	2	1
No lesions	5	11

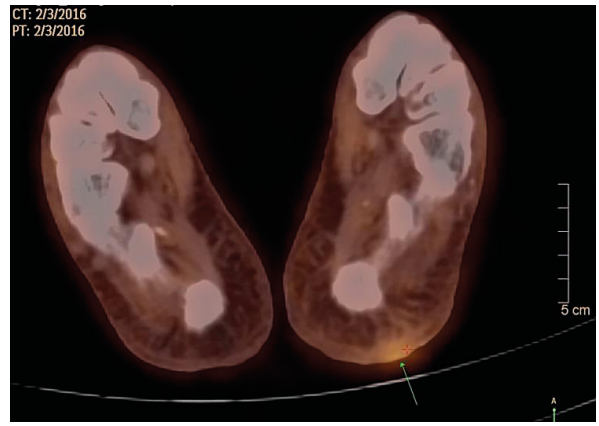

Figure 3. Staging of a cutaneous melanoma patient one month after tumor excision in the left foot, pT3b pN0 cM0. False positive skin thickening in the excision place, which was proven to be benign

Despite the high sensitivity (84.5%) of 18F-FDG PET/CT in the detection of regional lymph nodes, compared to 22.5% for CIS, 18F-FDG PET/CT failed to recognize 11 (1.1%) malignant lesions. All of them were non-significant lymph nodes, well recognized by further ultrasonography, which in those cases performed better than 18F-FDG PET/CT (Fig. 5).

Additionally, 18F-FDG PET/CT demonstrated 0.7% false positive results (FP), with 7 identified as malignant FP lesions: 3 DM, 2 metastatic regional lymph nodes, and 2 local recurrences (Fig. 3, 4), all proven FP by histology. The FP distant metastases (DM) were two cases of mediastinal lymph nodes due to sarcoidosis (Fig. 6) and one metabolically active hepatic lesion, all of them histologically proven benign.

Discussion

Cutaneous melanoma accounts for a small percentage of skin cancer cases but is responsible for the majority of skin cancer deaths. PET scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease. Most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma [4, 5]. In patients with stage III disease, 18F-FDG PET/CT may be more useful. In particular, 18F-FDG PET/CT scans can help to further characterize lesions found to be indeterminate on CT scan and can image areas of the body not studied by the routine body CT scans (i.e., arms and legs) [6, 7]. No randomized controlled studies (RCTs) comparing CT and 18F-FDG PET/CT in the staging of melanoma were identified. A meta-analysis by Xing et al. found that for staging of DM, 18F-FDG PET/CT had the highest sensitivity (80%, 95% CI = 53% to 93%), specificity (87%, 95% CI = 54% to 97%), and diagnostic odds ratio

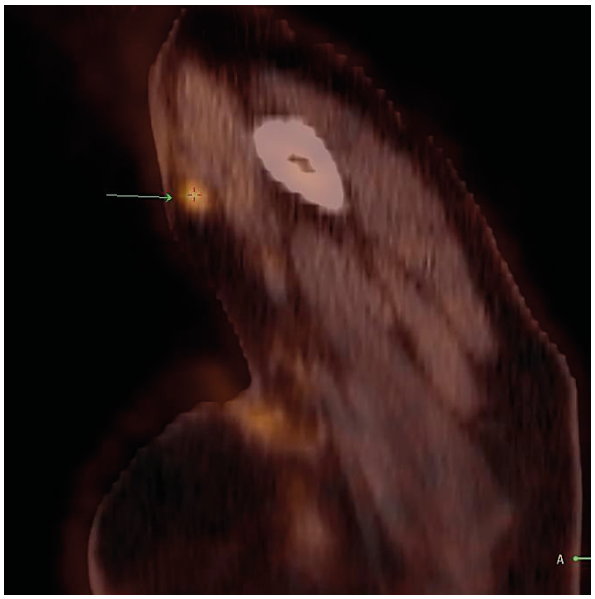

Figure 4. A patient with a right brachial cutaneous melanoma. 18F-FDG PET/CT was performed one month after axillary lymph node dissection for recurrent disease (rpN3b). A nodular lesion with high metabolic activity was found in the proximal brachium, suggesting a local recurrent disease. The latter was histologically proven benign granuloma

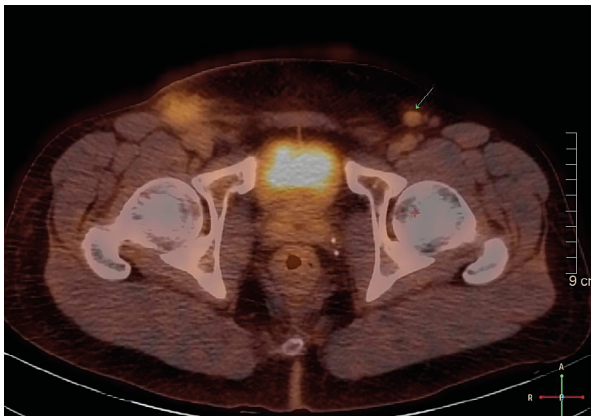

Figure 5. A patient with cutaneous melanoma of the trunk after excision of the primary tumor and right inguinal lymph node dissection, pT4b pN1b cM0. The patient was referred for an 18F-FDG PET/CT staging. There was a non-significant, but suspicious inguinal lymph node on the left, with no fatty center, with round shape, and metabolic activity slightly higher than the background. The patient was referred for an ultrasonographic exam and afterward for an excision

(25, 95% CI = 3.58 to 198.7) [8]. These results comply with our observation on 18F-FDG PET/CT sensitivity for DM, revealing 100% sensitivity compared to 12.3% for CIS. The specificity was good for both methods — 98.3% for 18F-FDG PET/CT and 94.5% for CIS.

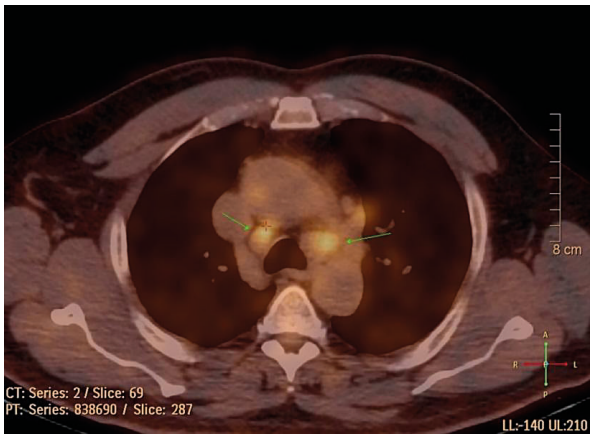

Figure 6. Patient with lower extremity cutaneous melanoma referred for restaging after recurrent disease. 18F-FDG PET/CT found mediastinal and symmetrical bilateral hilar lymphadenopathy, proven to be benign sarcoidosis

Systematic reviews on melanoma found 18F-FDG PET/CT to have a sensitivity of 68–87% and specificity of 92–98% in patients with stage III or stage IV disease [9] and specificity of 89% in patients with stage III disease [10]. According to most guidelines, 18F-FDG PET-CT should only be considered for patients with indeterminate findings on CT or for patients who are being considered for major surgical resection, after discussion with the specialist multidisciplinary team [11, 12]. NCCN recommends staging using 18F-FDG PET-CT from stage IIC whole-body examinations as an alternative to CT [13]. According to European Society for Medical Oncology (ESMO) recommendations, in IB–IIC stage CM 18F-FDG PET-CT, along with US for RLN, and/or CT, as well as brain magnetic resonance imaging (MRI), represent options for tumor extension assessment before surgical treatment and SLNB. Also, they recommend 18F-FDG PET/CT for staging only in very high-risk patients (pT3b and higher (III, C) [14]. The CM diagnosis and management recommendations from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization of Research and Treatment of Cancer (EORTC) [15] state that ultrasound is the best method to detect subclinical metastatic nodal disease, compared to palpation, CT, or 18F-FDG PET/CT, with the highest sensitivity (60%, 95% CI = 33% to 83%), specificity (97%, 95% CI = 88% to 99%), and diagnostic odds ratio (42, 95% CI = 8.08 to 249.8). The better sensitivity of 18F-FDG PET/CT in malignant lymph node recognition demonstrated an 84.5% detection rate in our study. It was possibly due to careful attention to regional lymph node basins which took into account their morphology, not only the metabolic activity, and further investigation of lymph nodes with oval or round shape, partly or fully

missing fatty hilum, and metabolic activity higher than the background. There are meta-analyses, confirming that 18F-FDG PET/CT is superior to CT for the diagnosis of DM or recurrence in restaging, but not during initial staging [16, 17].

The main role of US is in the diagnosis and follow-up of regional lymph nodes. US examinations have been shown to be superior to clinical examinations in the diagnosis of nodal metastases [15], but they may give false negative results in metastatic deposits smaller than 2 mm in size [18]. In the latest revision of the National Comprehensive Cancer Network (NCCN) 3.2022 recommendations, a new footnote states that US of lymph nodes requires specific radiologic expertise. Criteria for early nodal involvement by CM include the following features: hypoechoic island(s) in the cortex, asymmetric focal cortical thickening, and peripheral blood supply, especially when blood supply is established in areas of cortical thickening (Fig. 1). Core biopsy or aspiration biopsy of suspicious lymph nodes should be directed at the atypical areas in the cortex of the lymph node identified by US [13].

Sentinel lymph node biopsy is the gold standard for non-palpable lymph node staging in CM, which was also proven in our study, where 18F-FDG PET/CT found additional lesions only in patients with stage III disease after SLNB. Most guidelines do not recommend using 18F-FDG PET/CT in SLNB-positive patients because the yield is low in this setting (0.5–3.7%) [19]. Although American Academy of Dermatology (AAD) recommends PET-CT if the patient has nodal metastasis in SLNB (stage III). [12] In our study, 18F-FDG PET/CT detected additional malignant lesions in 12/28 patients (42.9%), which changed the stage and further management of the patients.

18F-FDG PET/CT also acted as an invaluable method for ITM recognition with 100% sensitivity, specificity, PPV, NPV, and accuracy. It was also able to reveal clinically not evident ITM in one patient in stage IIA, after negative SLNB. The superiority of SLNB over 18F-FDG PET/CT in detecting clinically not evident RLN has been previously discussed and confirmed in the literature [16]. ITMs occur in 2–10% of CM patients and are frequently associated with the development of nodal and/or systemic metastases [20], even in sentinel node-negative patients [21]. In our study, all of the ITM were identified, and all of them were smaller than 1 cm. All of them, except one, were detected in patients after surgical resection of locoregional recurrence. CM cells have high glutamine receptor activity and high levels of intracellular hexokinase. For this reason, CM has high avidity for the glucose analog ^{18}F-fluorodeoxyglucose (FDG) that is used for 18F-FDG PET/CT and is useful in detecting subcentimeter malignant lesions [22]. SLNB cannot detect in-transit metastases, which account for most locoregional recurrences [23]. High-frequency ultrasound is considered the best modality for detecting and diagnosing in-transit metastases due to its high accuracy in detecting smaller lesions [24, 25]. However, this technique has several limitations, including its dependence on operator skills, availability of an expert radiologist, and long study-performance time (at least 30–40 min for each limb or body area).

Conclusions

18F-FDG PET/CT is a key imaging method for staging and restaging patients with CM after complete resection of the recurrent locoregional disease, performing significantly better than CIS. The hybrid technique has a great advantage to detect DM disease and ITM in comparison to the conventional studies and must be used also in stage II patients as a baseline study after SLNB to exclude additional lesions. There is a high true positivity rate in the detection of malignant lymph nodes but still not enough to rely only on this method, mandating further SLNB and follow-up. This article underlines the complexity of the multimodality management of CM and also the need for further assessment of any suspicious lymph nodes detected by 18 F-FDG PET/CT in the draining LN basin with ultrasonography and/or biopsy.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Delays in the diagnosis of lung cancer patients in Poland

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ABSTRACT

Introduction. Lung cancer is the most common cause of death from malignant tumors in the world, with more than 2 million patients diagnosed every year. The most common symptoms of lung cancer are cough and shortness of breath. However, they appear late when the cancer is at an advanced stage. The standard measure of the correct diagnostic path in cancer patients is the time from the first symptoms of the disease to the final diagnosis. The aim of the study is to identify reasons for late diagnosis of patients with symptoms of lung cancer in Poland.

Material and methods. We performed an analysis of a survey conducted among 149 patients with lung cancer from the Department of Pneumonology, Oncology and Allergology at the Medical University of Lublin. The SPSS software was used to perform the analysis of these data. Males accounted for 56.4% of the patients, and the median age of the patients was 66.8 ± 7.2 years. The mean time from the first symptoms to the first appointment with a doctor was 5.3 weeks and from the first symptoms to diagnosis was 14.7 weeks.

Results. The time from the onset of symptoms and treatment initiation was significantly ($p = 0.04$) longer in patients living at a greater distance from cancer centers (24.1 weeks) than in patients living nearby (18.3 weeks). In patients who were treated with antibiotics before diagnosis, the time from the onset of the symptoms to the start of treatment was significantly longer ($p = 0.003$) than in patients who did not use antibiotics (26.8 weeks *vs.* 18.1 weeks).

Conclusions. The results of our study showed that Polish patients with suspected lung cancer are diagnosed too late, which has an impact on the stage at which the tumor is diagnosed.

Key words: delays, diagnosis, lung cancer, treatment, symptoms,

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Introduction

Lung cancer is the most common cause of death from malignant tumors in the world, with more than 2 million patients diagnosed every year. Annually, it is diagnosed in about 23000 Polish citizens while, according to the latest forecasts, in 10 years this number will rise to around 30000 per year. The incidence and mortality from lung cancer differ in individual countries, but the overall survival rate is low. According to the Surveillance, Epidemiology, and End Results (SEER) database, between 2012 and 2018, 5-year relative survival rates in non-small cell lung cancer (NSCLC), regardless of the disease stage, was 26%. However, the rate of small cell cancer (SCLC) was only 7%. For the whole population of lung cancer patients, 5-year relative survival was 22.9% [1, 2].

Unfortunately, the vast majority of patients are diagnosed at an advanced stage [3]. The low survival rate of lung cancer patients is due to long-term asymptomatic course of the disease and late initiation of diagnostic procedures. The incidence of lung cancer increases significantly among patients over the age of 65 years. Approximately 50% of all patients with lung cancer are at this age. This reflects the global increase in in life expectancy [4].

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The most common symptoms of lung cancer are cough (in over 90% of patients), shortness of breath, hemoptysis, chest pain, hoarseness, weakness, and weight loss [5]. As many as 80–90% of patients are former or current smokers [6]. Among men with lung cancer, 90% of the population were former or current smokers while 79% of women with this disease reported cigarette smoking. Nevertheless, the number of lung cancer patients who have never smoked is increasing [7].

Clinically, we distinguish SCLC (15% of lung cancer cases) and NSCLC (85% of lung cancer cases). Histologically, NSCLC is classified into adenocarcinoma (35–40%), squamous cell carcinoma (30%), large-cell carcinoma (2%), and other rare types of neoplasm. In the treatment of SCLC, chemoradiotherapy is used in limited disease (LD), whereas for patients with extensive disease (ED), either chemotherapy or chemoimmunotherapy is used. In the treatment of an early stage of NSCLC, surgery may be used seldom, which often is supplemented with preoperative chemotherapy or adjuvant chemotherapy. Chemoradiotherapy with the option of consolidating immunotherapy is used in the treatment of locally advanced NSCLC. These therapeutic methods can be used only in 20–25% of patients, depending on the stage of the disease, performance status of patients, and comorbidities. The therapeutic methods used in the treatment of advanced lung cancer include chemotherapy, molecularly targeted therapies, and immunotherapy, as well as a combination of these methods of treatment [8].

In this study, we present the preliminary results on reasons for delays in the diagnosis of patients with lung cancer.

Material and methods

An analysis was performed of patients with lung cancer diagnosed and treated in the Department of Pneumonology, Oncology and Allergology at the Medical University of Lublin. Patients were enrolled in the study in 2021 and 2022 and asked to complete a survey designed by the authors and composed of 29 questions. So far, 149 adult patients have been included in the study, regardless of the histological type of cancer and treatment modality applied.

Quantitative variables are represented by mean ± standard deviation (SD). The consistency of the distribution of continuous variables with the normal distribution was confirmed using the Kolmogorov-Smirnov test. The statistical significance of the differences between the mean values of independent continuous variables with a normal distribution was assessed with Student's t-test and the independent variables with the distribution inconsistent with the normal distribution using the Mann-Whitney U test. Categorical variables were compared using Pearson's chi-square test. $P < 0.05$ was adopted as statistically significant. All calculations were performed with the SPSS software.

All patients were informed about the purpose of the study and gave their written consent to participate in it. The study was approved by the local Bioethics Committee at the Medical University of Lublin (approval number — KE-0254/14/2021).

Results

In total, 149 patients were included in the study. The majority were males (56.4%), and the median age was 66.8 ± 7.2 years (range from 39 to 85 years). The mean BMI (body mass index) of the patients was 26.3 ± 4.7, and 19% of the patients were obese (BMI over 25). The vast majority of patients (89.9%) were in very good or good general condition [performance status (PS) according to World Health Organization (WHO) classification: 0 or 1].

The majority of patients (73%) inhabited rural areas. Over 50% of the respondents lived in distant areas (> 5 km) from primary health care (Tab. 1).

Cigarette smokers were the majority (116 respondents, 77.9%) of the total population, and 73.3% of this group were current cigarette smokers. Former smokers were defined as those who had not smoked for at least 5 years. Small-cell carcinoma was diagnosed in 15.4% of patients, and NSCLC in 76.5% of patients. At diagnosis, 80.5% of patients had distant metastases.

Table 1. Epidemiological characteristics of patients in relation to the distance from the general practice (GP)

	Home close to a general practice n = 71 (48%)	Home far from a general practice n = 78 (52%)	p
Age (years)	67.5 ± 7.3	66.2 ± 7.0	0.273
BMI (kg/m^2)	26.2 ± 4.6	26.3 ± 4.9	0.834
Time from the first symptoms to the first GP appointment (weeks)	6.7 ± 14.9	4.1 ± 7.9	0.8
Time from the first symptoms to diagnosis (weeks)	16.9 ± 16.5	12.7 ± 12.2	0.082
Time from symptoms to start treatment (weeks)	18.3 ± 13.0	24.1 ± 17.1	0.041

In 15.4% of patients with non-squamous NSCLC, mutations in the *EGFR* gene were found while rearrangements of the *ALK* or *ROS1* genes were seen in 4.6% of patients. PD-L1 expression on tumor cells was found in 86% of patients with NSCLC, and in 27.2% of patients, high expression of PD-L1 was diagnosed (≥ 50% of tumor cells with PD-L1 expression).

Surgery was performed in 24 patients (16.1%). Radiotherapy was used in 34.9% of patients while 83.1% of patients received chemotherapy, including 77.2% of patients who were treated with platinum-based regimens. In 16% of patients, molecularly targeted therapies were used. In patients treated with these therapies, osimertinib (25%), erlotinib (18.8%), and crizotinib (18.8%) were most often used. In 44.3% of patients, immunotherapy was administered (monotherapy or in combination with chemotherapy). Pembrolizumab was most commonly used (23% of patients). Immunotherapy in the first-line treatment was used in 15.6% of patients and in the second-line therapy — in 24.5% of patients. Thirty-one point five percent of patients had been treated with at least one antibiotic up to six months before diagnosis.

Symptoms of lung cancer were found in 71.8% (Tab. 2). The most common was cough (31.8%). Twelve point five percent had general symptoms at the time of diagnosis.

The mean time from the symptom onset to the first medical appointment was 5.3 ± 11.8 weeks. More than half (55.7%) of patients reported to their general practitioner (GP) with the first, disturbing symptoms. The time from the development of the first symptoms to diagnosis was 14.7 ± 14.6 weeks. The mean time from the first symptoms to the first chest X-ray examination was 6.8 ± 12.1 weeks. Mean time from the onset of symptoms to the chest computed tomography (CT) exam was 10.8 ± 13.8 weeks (Tab. 3).

The mean time from CT examination to bronchoscopy was 24.1 ± 26.2 days, and from bronchoscopy to pathological diagnosis was 20.3 ± 29.5 days. The time from receiving the pathomorphological results to the examination of predictive factors (*EGFR* mutations, *ALK,* and *ROS1* rearrangements, as well as PD-L1 expression testing in non-squamous NSCLC or only PD-L1 expression testing in squamous NSCLC) was 13.8 ± 25.4 days. The duration of the examination of predictive factors was on average 7.6 ± 7.4 days. The

Table 2. Presence of symptoms of lung cancer in analyzed patients

	Men	Women	p, χ^2
Presence of symptoms	63 (75%)	44 (68%)	p = 0.325 χ^2 = 0.967
Cough	17 (20%)	17 (26%)	p = 0.395 χ^2 = 0.728
General symptoms	15 (18%)	4 (6%)	p = 0.03 χ^2 = 4.511
Respiratory symptoms	45 (54%)	40 (62%)	p = 0.329 χ^2 = 0.949
More than one symptom	11 (13%)	14 (22%)	p = 0.171 χ^2 = 1.871
Infection treated < 6 months before diagnosis	29 (35%)	18 (28%)	p = 0.373 χ^2= 0.792

Table 3. Numbers and percentages of patients with and without delay in lung cancer diagnosis

	Average (weeks)	Without delay (n, %)	< 1 month (n, %)	1–6 months (n, %)	> 6 months (n, %)
Time from first symptoms to diagnosis	14.7	42 (28.2%)	11 (7.4%)	65 (43.6%)	31 (20.8%)
Time from first symptoms to first medical appointment	5.3	54 (36.2%)	49 (32.9%)	34 (22.8%)	12 (8.1%)
Time from first symptoms to first X-ray	6.8	42 (28.2%)	30 (20.1%)	45 (30.2%)	32 (21.5%)
Time from first symptoms to first CT	10.8	39 (26.2%)	22 (14.8%)	67 (45%)	21 (14.1%)
Time from first symptoms to visit a consultant	7.3	72 (48.3%)	23 (15.4%)	40 (26.8%)	14 (9.4%)

CT — computed tomography

time from bronchoscopy to final diagnosis and therapeutic decision was 34.3 ± 36.8 days. The mean time from the onset of symptoms to the start of treatment was 21.0 ± 15.3 weeks. The time from bronchoscopy to the start of treatment was 41.1 ± 17.6 days, and from histopathological results to the start of treatment was 38 days (Fig. 1).

The time from the onset of treatment was significantly ($p = 0.04$) longer in patients living in areas further from cancer centers (24.1 weeks) than in patients living nearby (18.3 weeks). Another statistically significant difference ($p < 0.001$) concerned the time from the first symptoms to diagnosis, which was longer in patients receiving antibiotics (20.3 weeks) compared to patients without this treatment (12 weeks). Furthermore, in patients who had been treated with antibiotics before diagnosis, the time from the onset of first symptoms to the start of the treatment was statistically significantly longer ($p = 0.003$) than in patients who did not use antibiotics (26.8 weeks *vs.* 18.1 weeks). Patients treated with antibiotics had a significantly ($p < 0.03$) longer time from the first symptoms to the first visit to a consultant (10.5 weeks *vs.* 5.7 weeks) and to the first CT examination (15.5 weeks *vs.* 8.5 weeks) compared to patients who had not been treated with antibiotics (Tab. 4).

Discussion

Although diagnostic and therapeutic strategies have improved in recent years, lung cancer remains the leading cause of cancer death worldwide. Patients often report to their GP late, which may partly result in a higher mortality rate. Mitchell et. al. [9] demonstrated that delays in diagnosis of lung cancer are mainly due to the failure to recognize abnormalities visible on chest X-ray and failure to perform key diagnostic procedures at the right time. Schabath et. al. [10] indicated that quick diagnosis and access to effective modern methods of treatment are important determi-

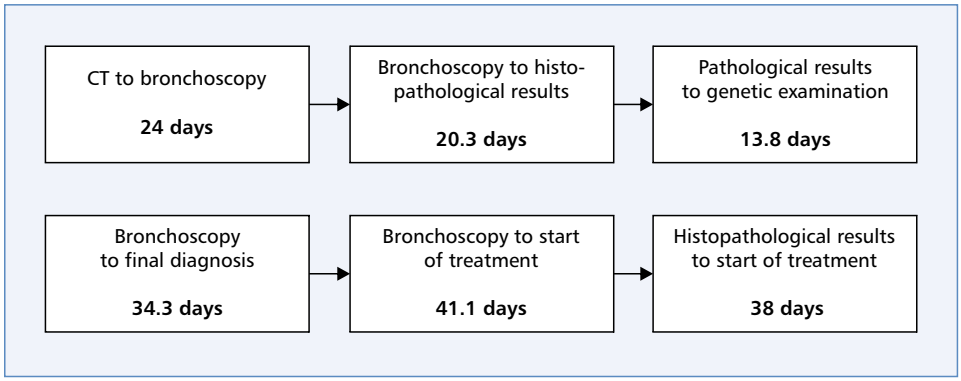

Figure 1. Duration of the diagnostic process from the first computed tomography (CT) examination in lung cancer patients

Table 4. Duration of individual diagnostic stages in patients who had received and had not received antibiotics before cancer diagnosis

	Patients treated with antibiotics 6 months before cancer diagnosis	Patients not treated with antibiotics 6 months before cancer diagnosis	p
Time from the first symptoms to the first medical appointment (weeks)	7.5	4.3	0.005
Time from the first symptoms to diagnosis (weeks)	20.3	12	< 0.001
Time from symptoms to the start of treatment (weeks)	26.8	18.1	0.003
Time from the first symptoms to the first visit to a visit a consultant (weeks)	10.5	5.7	0.003
Time from the first symptoms to the first X-ray examination (weeks)	9.9	5.3	0.004
Time from the first symptoms to first computed tomography (weeks)	15.5	8.5	< 0.001

nants of cancer patient outcomes. Higher indicators of survival for patients with lung cancer are observed in high-efficiency healthcare systems. Patients in Japan or Israel have much higher five-year survival rates (33% and 27%, respectively) than patients from Bulgaria, Poland, or Brazil (10%). Early diagnosis contributes to reducing mortality due to early initiation of treatment [10]. Early diagnosis also limits financial outlays. Total direct healthcare expenditure related to lung cancer is significant. In the United States, the total estimated medical cost of lung cancer diagnosis and treatment was $12.1 billion in 2010 and was expected to increase to $15.2 billion in 2020 [11]. Additionally, prompt cancer diagnosis to improve therapeutic outcomes is a priority for many European governments. For example, the UK government policy focuses on increasing the proportion of cancers diagnosed early (i.e. in stage 1 or 2) from half to three-quarters by 2028 [12].

According to the National Institute for Health and Care Excellence (NICE) guidelines, the time from the manifestation of disturbing symptoms observed by a physician to performing a chest X-ray or referral to a specialist doctor with suspicion of lung cancer should be 2 weeks or less [13]. Meanwhile, our study showed that in Poland the average waiting time for an appointment with the specialist was 7.3 weeks, and the time to the first X-ray was 6.8 weeks. The time from the onset of symptoms to the first GP visit was 5.3 weeks. This may be due to the fact that the symptoms are ignored by patients and by physicians (e.g. due to similarity in symptoms of lung cancer and chronic diseases, such as chronic obstructive pulmonary disease, as well as insufficient access to GPs in Poland). A study at Turku University Hospital in Finland showed that the time from first symptoms to diagnosis was 98 days, between the first visit to a GP and diagnosis — 52 days, and 15 days from the specialist visit to diagnosis [14].

The Cancer Care Ontario guidelines state that patients with suspicion of lung cancer on X-ray or with a high clinical probability of cancer should be referred for a chest CT scan within two weeks. They should wait no longer than 2 weeks for an appointment with a specialist [15]. According to the British Thoracic Society, the results of the histopathological examination should be completed within 2 weeks from the time of sample collection. The presence of predictive factors should be determined within 2 weeks. In patients in the early stage of NSCLC, surgery should be performed within a maximum of 8 weeks from qualification. If necessary, adjuvant chemotherapy should be given within 120 days after surgery. Chemotherapy should be given within 7 days from the treatment decision [16]. On the other hand, a study from Canada showed that the average total waiting time from the appearance of the first symptoms to the start of treatment was 4.5 months [17]. These results are comparable to those obtained in our study.

Lung cancer screening can reduce the relative risk of dying from lung cancer by 20%, but when combined with smoking cessation, this benefit has been estimated to be as high as 38%. Smoking cessation reduces the risk of dying from lung cancer, but it is known that the risk of lung cancer in ex-smokers is still higher compared to non-smokers. The relative risk of developing lung cancer is low if smoking was stopped at a young age [18]. Intensive anti-smoking campaigns are needed, as well as encouragement from primary healthcare workers. Each patient presenting with respiratory symptoms should undergo the Fagerström test, and they should be informed about the harmful effects of smoking. In some cases, anti-nicotine therapy should also be administered. As the number of smokers decreased, there was an overall decrease in the incidence of lung cancer. However, despite the overall reduction in the incidence of this cancer, a significant increase in the incidence of lung cancer among non-smokers was noted [19]. Several studies have suggested that lung cancer in non-smokers differs from smoking-induced lung cancer in both biological and epidemiological terms, and it should therefore be considered as an entirely separate entity. The term "non-smoker" classically refers to people who have smoked less than 100 cigarettes in their lifetime. Regarding the type of cancer, NSCLC (mainly adenocarcinoma) is more common in non-smokers. Studies have shown that lung cancers in non-smokers are much more common in women. Worldwide, 15–20% of men and up to 50% of women diagnosed with lung cancer have never smoked. This demographic group has significant geographic variations, as 60–80% of Asian women with lung cancer have never smoked. In a US study, approximately 19% of women and only 9% of men with lung cancer were non-smokers [20].

In our study, as many as 31.5% of patients had been treated with antibiotics due to respiratory tract infections prior to cancer diagnosis. Most patients had been treated with at least one antibiotic; in one case, before the lung cancer diagnosis, the patient had been prescribed 7 antibiotics (from different groups). These patients had no evidence of inflammation, (e.g. fever), and the symptoms they reported to their GPs were cough, shortness of breath, and hemoptysis. General practices ordered laboratory and imaging tests and referred them to a pulmonologist after the antibiotic treatment failure. This situation prolonged the diagnostic and therapeutic process by several weeks. According to the literature, symptoms of a respiratory tract infection may mask the developing neoplasm [21]. As shown in a study conducted in Sweden in 2009–2016, pneumonia may be an early symptom of lung cancer, and it is often the subject of differential diagnosis of this disease. Compared to healthy subjects, significantly more patients received at least one antibiotic treatment in the three years prior to diagnosis of cancer. Patients

diagnosed with lung cancer were twice as likely to take at least one antibiotic compared to healthy controls. Importantly, 7% of lung cancer patients had used at least four courses of antibiotic therapy in the three years prior to cancer diagnosis, which may suggest inappropriate and too frequent prescribing of these drugs [22, 23].

Respiratory tract infections often precede the diagnosis of lung cancer. In addition, chronic pulmonary obstructive disease and infections are more common in smokers, who have a higher risk of lung cancer, and take antibiotics more often due to an exacerbation [24]. Particular oncological vigilance should be undertaken when no improvement is observed after the use of an antibiotic in a patient with cough or dyspnea, or the improvement is temporary and slight. The occurrence of hemoptysis should always result in referring the patient to a specialist. After the failure of the first-line antibiotic therapy, diagnostics methods should be extended to imaging examinations or the patients should be referred to a pulmonologist.

Conclusions

The results of our study showed that patients with suspicion of lung cancer are diagnosed with considerable delay in Poland, which has an impact on the disease stage and patient' performance status at the final diagnosis. The vast majority of delays in the Polish healthcare system occur before and during a visit to the general practitioner. This study found that most patients experienced long delays between the first examinations carried out in connection with suspected lung cancer and the final diagnosis. Therefore, most of the patients were diagnosed at advanced stages of the disease. Treatment costs of lung cancer increase significantly with the higher stages at which the cancer is diagnosed. Procedures that diagnose lung cancer at an earlier stage can allow for lower resource consumption and costs of treatment. Algorithms for managing a patient with symptoms of lung cancer should be directed to physicians.

Systemic changes are necessary for patients to be diagnosed quickly and efficiently. Patients in Poland have access to most of the latest therapeutic methods used in the world. Thanks to this, we can classify lung cancer as a chronic disease. In the future, we plan to conduct a survey among another 200–250 people and also extend the results to aspects such as overall survival or progression-free survival, depending on the time of diagnosis and treatment methods.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Patterns of multiple primaries in fortyfour cancer patients: a single-center clinical experience

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ABSTRACT

Introduction. Multiple primaries are defined as the existence of more than one synchronous or metachronous cancer type in the same individual. Due to a longer follow-up time after a primary cancer diagnosis, the likelihood of detection of a second primary is also increased. We report on patterns of multiple primaries in a cohort of cancer patients from a single institution.

Material and methods. We identified 44 patients with multiple primaries that were diagnosed, treated, and followed up between March 2011 and January 2022 from our prospectively maintained database at the Hatay Education and Research Hospital Cancer Unit.

Results. The median follow-up time was 60 months (range; 3–103). The median time between the diagnosis of the first primary and the second primary was 29 months (range; 0–94). The median OS was 76 months (95% CI 26.6–125.4) from the first diagnosis and 27 months (95% CI 0.65–53.4) from the diagnosis of the second primary for the entire cohort. The first diagnosed tumor was localized in the gastrointestinal system in 43.2% of patients and 65.9% of all tumors were adenocarcinoma. The first diagnosed cancer was at an early stage (Stages I and II) in 63.6% of patients. At the staging evaluation of the second primary, 54.5% of patients were found to be in the early stage (Stages I and II) and 45.5% were found to be in the late stage (Stages III and IV).

Conclusions. Our study is important as this is the largest cohort study about practical implications of managing multiple primaries. The risk of second and further primaries should be kept in mind in the active follow-up Introduction and surveillance of cancer patients .

Key words: carcinoma, invasive cancer, multiple primaries, pattern, survival

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Introduction

Cancer remains a global health problem with over 18 million new cases and 9.6 million deaths in 2018 [1]. It is the second major cause of death in the United States [2]. The lifetime probability of being diagnosed with an invasive cancer is about 40% [2]. Cancer survival has improved in the last decades, and the 5-year relative survival rate is approximately 67% for all cancers [2]

Multiple primaries are defined as the existence of is the second major cause of death in the United States more than one synchronous or metachronous cancer [2].

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The lifetime probability of being diagnosed with an type in the same individual. Synchronous refers to the time interval of fewer than 6 months between the two diagnoses, whereas metachronous refers to the time interval of more than 6 months. Due to a longer follow-up time after a primary cancer diagnosis, the likelihood of detection of a second primary has also increased. Moreover, persisting genetic and environmental risk factors and toxic effects of therapies can lead to second and further primaries in cancer patients. The reported frequency of multiple primary cancers is in the range of 2–17% [3–7].

Although there are many epidemiological studies and multi-institutional reports on the frequency of multiple primaries from different countries, there is no study about how to manage multiple primaries in daily clinical practice.

In the present study, we aimed to evaluate the patterns of multiple primaries in a cohort of cancer patients from a single institution. To the best of our knowledge, this is the largest cohort that includes all types of cancers, and all pathological specimens were evaluated in the same clinic.

Material and methods

Patients

A total of 44 cancer patients with multiple primaries that were diagnosed, treated, and followed up between March 2011 and January 2022 were identified in our prospectively maintained database at the Hatay Education and Research Hospital Cancer Unit. The study was carried out with the local ethics committee's approval (meeting number: 10, decision number: 09, date: 03/09/2020).

Diagnosis, staging, and follow-up

All patients had an imaging study, such as computer tomography (CT) or positron emission tomography (PET)/CT scan, as a staging workup. Overall survival (OS) was calculated as the time interval from the date of the first cancer diagnosis to death or loss to follow-up. Patients who were lost to follow-up were censored on that date. After the completion of therapy, patients were followed up at 3- to 6-month intervals in the first 2 years and then less frequently until the completion of 5 years or a patient's death.

Statistical analysis

The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses. The Kolmogorov-Smirnov test was performed for assessing the normality of the distribution of numerical variables. The normally distributed numerical variables were expressed as mean ± standard deviation (SD). The non-normally distributed numerical variables were expressed as median (minimum-maximum). The categorical variables were expressed as frequency (percentages). The Kaplan-Meier analysis and the log-rank test were used to analyze and compare OS. A two-sided p-value < 0.05 was considered significant.

Results

The demographic, clinical, and pathological characteristics of 44 patients are summarized in Table 1. Most of the patients were male (54.5%), and the median age at diagnosis was 61.5 years (range; 18–86). Most of the patients were older than 60 years (61.4%).

The median follow-up time was 60 months (range; 3–103). The median time between the diagnosis of the first primary and the second primary was 29 months (range; 0–94). At the last analysis, 23 patients died. Median OS was 76 months (95% Cl 26.6–125.4) from the first diagnosis and 27 months (95% Cl 0.65–53.4) from the diagnosis of the second primary for the entire cohort. The 2- and 5-year OS rates were 75% [20.4 months (95% CI 18.3–22.4)] and 54.5% [42.4 months (95% CI 36.1–48.8)] (Fig. 1), respectively.

Table 2 shows the 5-year overall survival analysis according to age and sex. Median OS was longer in female patients compared to male patients but did not reach a significant value [49.5 months (95% CI 43.2–55.7) *vs.* 36.6 months (95% CI 26.7–46.4), p = 0.26] (Fig. 2). Median OS was also non-significantly longer for patients younger than 60 years compared to patients older than 60 years [47.3 months (95% CI 38.3–56.3) *vs.* 39.4 months (95% CI 30.9–47.9), p = 0.26] (Fig. 3).

Patterns of primarily diagnosed cancer

The first diagnosed tumor was localized in the gastrointestinal system in 43.2% of patients, and 65.9% of all tumors were adenocarcinomas. The first diagnosed cancer was at an early stage (Stages I and II) in 63.6% of patients.

Patterns of secondarily diagnosed cancer

A complete restaging evaluation with CT or PET/CT scan and with biopsies was performed in all patients at the diagnosis of the second primary. The localization of the second primary was the gastrointestinal system, lung, and prostate in 25.1%, 18.2%, and 13.6% of patients, respectively. The histology of the second primary was adenocarcinoma in 54.6% of patients. At the staging evaluation of the second primary, 54.5% of patients were found to be in the early stage (Stages I and II), and 45.5% were found to be in the late stage (Stages III and IV).

Table 1. Demographic, clinical and pathological characteristics of patients

Age (mean ± SD)	61.30 ± 16.02		
Age			
< 60	17 (38.6%)		
≥ 60	27 (61.4%)		
Sex			
Male	24 (54.5%)		
Female	20 (45.5%)		
Location of first primary tumor	n (%)	**Location of second primary tumor**	n (%)
Colon	8 (18.2%)	Lung	8 (18.2%)
Rectum	5 (11.4%)	Prostate	6 (13.6%)
Skin	5 (11.4%)	Colon	5 (11.4%)
Breast	4 (9.1%)	Skin	4 (9.1%)
Gastric	3 (6.8%)	Breast	4 (9.1%)
Prostate	3 (6.8%)	Rectum	4 (9.1%)
Lip	2 (4.5%)	Lymph	3 (6.8%)
Bladder	2 (4.5%)	Kidney	2 (4.5%)
Brain	2 (4.5%)	Thyroid	2 (4.5%)
Ovary	1 (2.3%)	Ureter	1 (2.3%)
Endometrium	1 (2.3%)	Appendix	1 (2.3%)
Kidney	1 (2.3%)	Bladder	1 (2.3%)
Lymph	1 (2.3%)	Ovary	1 (2.3%)
Pancreas	2 (4.5%)	Gastric	1 (2.3%)
Esophagus	1 (2.3%)	Endometrium	1 (2.3%)
Thyroid	1 (2.3%)		
Nasopharynx	1 (2.3%)		
Cervix	1 (2.3%)		
Pathology of first primary tumor	**n (%)**	**Pathology of second primary tumor**	**n (%)**
Adeno carcinoma	25 (56.8%)	Adeno carcinoma	20 (45.5%)
Invasive ductal carcinoma	4 (9.1%)	Invasive ductal carcinoma	4 (9.1%)
SCC	3 (6.8%)	NHL	3 (6.8%)
BCC	3 (6.8%)	BCC	2 (4.5%)
Urothelial carcinoma	3 (6.8%)	Urothelial carcinoma	2 (4.5%)
Glioblastoma	2 (4.5%)	SCC	2 (4.5%)
Serous carcinoma	1 (2.3%)	RCC	2 (4.5%)
RCC	1 (2.3%)	Papillary carcinoma	2 (4.5%)
NHL	1 (2.3%)	Small cell carcinoma	2 (4.5%)
Papillary carcinoma	1 (2.3%)	NET	2 (4.5%)
		Non-small cell carcinoma	2 (4.5%)
		Serous carcinoma	1 (2.3%)
Stage of first primary tumor	**n (%)**	**Stage of second primary tumor**	**n (%)**
Stage I–II	28 (63.6%)	Stage I–II	24 (54.5%)
Stage II–IV	16 (36.4%)	Stage III–IV	20 (45.5%)
Median follow-up time from the first primary tumor (min–max)	60 (3–103)	**Median follow-up time from the secondary primary tumor (min–max)**	24 (2–97)
Died		23 (52.3%)	

SD — standard deviation; BCC — basal cell carcinoma; SCC — squamous cell carcinoma; RCC — renal cell carcinoma; NHL — non-hodgkin lenfoma; NET — neuroendocrine tumor

Discussion

In the present study, we showed that even in cancer patients who are in active follow-up second primary cancers are mostly detected in the late stages. This can be related to an increased focus on the first primary.

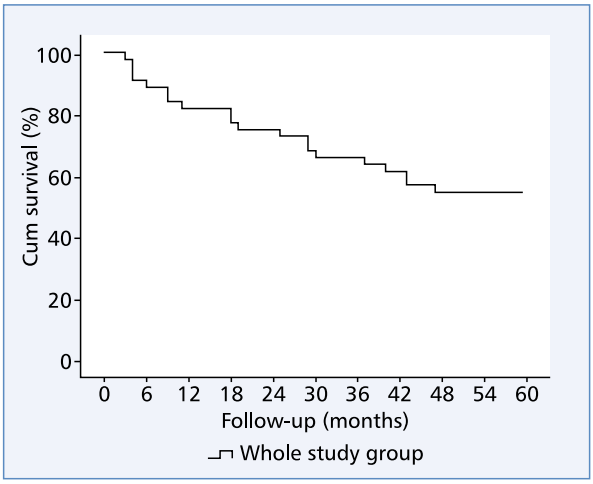

Figure 1. Kaplan-Meier curves for 2-year and 5-year overall survival

Multiple primaries were defined differently by the SEER (Surveillance, Epidemiology, and End Results) Program and the IACR/IARC (International Association of Cancer Registries and International Agency for Research on Cancer) [6, 7]. There are two main differences between these definitions. First, the time to distinguish between synchronous and metachronous multiple primaries, the IACR/IARC recommends 6 months while the SEER database suggests 2 months. Second, the tumors located in the different part of an organ, while the SEER database considers tumors located in different parts of the same organ as different tumors, the IACR/IARC evaluates the organ as a whole without segmenting it. Persisting genetic and environmental risk factors and toxic effects of therapies can lead to second and further primaries in cancer patients.

In a recent pilot study, Saegobin et al. [8] assessed the implications of cancer-related therapy in the development of a new primary. They found that 24 of a total of 602 patients had a second cancer within 5 years from the diagnosis of the first primary. In conclusion, they reported no increased risk of the second primary after exposure to different kinds of cancer therapies. Likewise, in our cohort, the development of the second

Table 2. 5-year overall survival analysis according to age and sex

	5-year OS rate	Survival time (month)	95% CI		Log-rank	
			Upper	Lower	Chi-square	P-value
Age < 60	64.7%	47.3 ± 4.6	38.3	56.3	1.277	0.258
Age ≥ 60	48.1%	39.4 ± 4.4	30.9	47.9		
Male	50%	36.6 ±5.1	26.7	46.4	1.283	0.257
Female	60%	49.5 ± 3.2	43.2	55.7		

OS — overall survival; CI — confidence interval

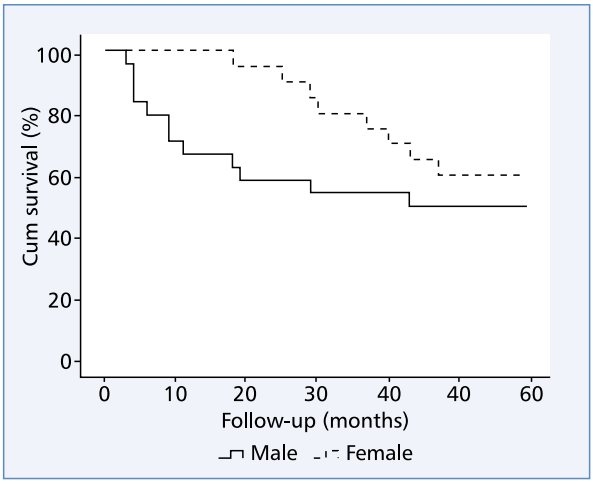

Figure 2. Kaplan-Meier curves for 5-year overall survival according to sex

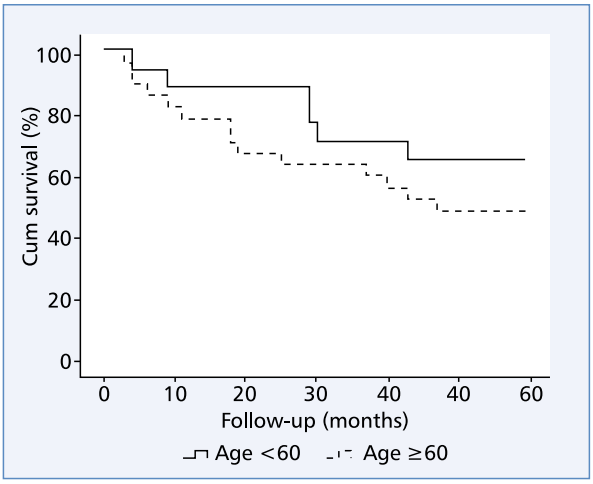

Figure 3. Kaplan-Meier curves for 5-year overall survival according to age

primaries did not seem to be related to the therapy of the first primaries.

The median time between the diagnosis of the first and second primary in our study was fewer than 3 years. It is less than the previously reported 5–10 years [8]. This can be related to the increased median age in our cohort.

Some population-based studies evaluated the incidence of second primaries in different parts of the world [3, 9, 10]. These population-based studies can identify genetic and environmental risk factors that can cause multiple primaries. However, none of these reports showed a specific risk factor that can be the cause for multiple primaries. Some other studies are designed to assess the frequency of multiple primaries in a specific body part such as gynecologic malignancies, and the colorectal or aerodigestive tracts [11–17]. The reports evaluating the effect of cancer treatment on the development of second primaries demonstrated that both chemotherapy and radiotherapy can cause secondary primaries [18–23].

The present analysis has some limitations such as being a retrospective and single-center study. The retrospective nature of the study made it impossible to elucidate the exact relation between different primaries. Well-designed, prospective studies will help to identify causes and optimum follow-ups of multiple primaries.

Conclusions

Our study is important as this is the largest cohort study about practical implications of managing multiple primaries. The risk of second and further primaries should be kept in mind in the active follow-up and surveillance of cancer patients.

Informed consent

Since the current investigation focused on retrospective data collection, no informed consent was required. Nonetheless, we acquired legal authorization from the Hospital Managers, laboratories, local and state Health Secretariats to access databases, laboratory, and medical records.

Conflict of interest

The authors have no conflicts of interest to declare for this study.

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None.

Authors contribution

The authors confirm contribution to the paper as follows: Conceptualization: MED; Formal Analysis: TK, MS, OI; Investigation: MC, AB, YMB; Methodology: MED, DMK, MS; Project Administration: OI, CK; Writing — Original Draft: MED, DMK, YMB, CK; Writing — Review & Editing: All authors.

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VIA MEDICA

ORIGINAL ARTICLE

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Circulating microRNAs as a potential diagnostic marker in chronic pancreatitis, pancreatic cancer and colorectal cancer

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ABSTRACT

Introduction. We evaluated the expression of selected circulating microRNAs (miRNAs) in chronic pancreatitis (CP), pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC) patients and healthy volunteers to test for differences in their levels and potential use as biomarkers.

Material and methods. A study of plasma miRNAs expression was performed in 88 patients: 40 (45%) CP patients, 20 (23%) PDAC patients, and 28 (32%) CRC patients. Expression of miRNA-17-5p, miRNA-93-5p, miRNA-320a-5p, miRNA-519d-3p, miRNA-526b-3p, and miRNA-5590-3p was assessed by the qRT-PCR method.

Results. Higher expression of miRNA-93-5p was observed in patients with PDAC ($p = 0.02$) and CRC ($p = 0.005$) compared to healthy individuals. Lower expression of miRNA-519d-3p was found in PC ($p = 0.01$) and PDAC ($p = 0.02$) compared to healthy volunteers. Higher expression of miRNA-93-5p was observed in patients with CP who had a higher concentration of CA-19-9 compared to patients with a low level or unknown status of this marker ($p = 0.03$). Examination of miRNA-519-3p expression distinguished patients with CP from healthy volunteers with sensitivity and specificity of 60% and 80%, respectively. Testing miRNA-93-5p and miRNA-519 expression distinguished PDAC patients and healthy participants with sensitivity and specificity of 60% and 77% (for miRNA-93-5p examination), as well as 59% and 79% (for miRNA-519-3p examination). Examination of miRNA-17 and miRNA-93-5p distinguished CRC patients and healthy donors. Sensitivity and specificity of this test were 78% and 50% for miRNA-17 examination, as well as 78% and 80% for miRNA-93-5p examination.

Conclusions. Our data indicate that miRNA-93, miRNA-17, and miRNA-519 demonstrate potential as biomarker molecules in the diagnosis of CP, PDAC, and CRC.

Key words: biomarkers, chronic pancreatitis, colorectal cancer, microRNA, pancreatic cancer

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Introduction

Cancer has become a global health problem resulting in a shortened life and lowering its quality. Among all gastrointestinal cancers, two of them come to the fore: colorectal cancer, due to high incidence concerning environmental factors, and pancreatic ductal adenocarcinoma (PDAC) because of poor prognosis [1]. The last one may be confused with chronic pancreatitis (CP) due to similarity in the clinical course and imaging studies.

Chronic pancreatitis is a disease that, due to its slow oligosymptomatic course in an early phase, causes many diagnostic problems. In 2016, a new mechanistic definition of CP was proposed, which was accepted by the majority of international gastroenterological societies. According to this definition, CP is a pathologic fibro-inflammatory syndrome of the pancreas with genetic, environmental, and/or other risk factors. It leads to parenchymal injury or stress. As a consequence of injury, exocrine and, in the latest stage, endocrine insufficiency develops [2].

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Chronic pancreatitis is also associated with the risk of pancreatic ductal adenocarcinoma (PDAC), higher than in the general population. Patients with CP have a nearly 8-fold increased risk of developing pancreatic cancer five years after diagnosis [3]. Until now little is known about this relationship although some *in vivo* studies indicated a significant role of interleukin-22 (IL-22) in the promotion of PDAC development [4].

Pancreatic ductal adenocarcinoma is a highly aggressive disease with a poor prognosis and rising incidence and with an average 5-year survival rate of less than 10% [5]. Enlargement of the pancreas (tumor-like mass) with inflammation in the course of CP may mimic PDAC at imaging, which precludes pre-operative diagnosis and may lead to unnecessary surgical intervention [6]. Moreover, these two pathologies show similar biochemical parameters and clinical manifestations [7]. For these reasons, there is an urgent need to identify non-invasive markers that help distinguish PDAC from CP because all available serological and imaging examinations are non-specific for these diseases.

Colorectal cancer (CRC) is now the third most common cancer in the western world. According to the World Health Organization, 1.8 million new cases of CRC in 2018 were diagnosed, and 862 000 patients died from CRC [8]. Although we have screening tools, most notably colonoscopy, many colorectal cancers are diagnosed in advanced stages. A better understanding of pathological and molecular mechanisms of CRC may provide new perspectives for cancer prevention and care.

The non-coding microRNAs (miRNAs) seem to be promising and valuable markers of cancer development. These molecular players, 18–25 nucleotides in length, are involved in various biological processes, including cell proliferation, apoptosis, differentiation, and metabolism. MicroRNAs function is post-transcriptional regulation of gene expression complementary linkage to sequences within mRNA molecules (most often to untranslated regions). As a result, these mRNAs are silenced, and the expression of the proteins they encode decreases. Therefore, miRNAs could act as oncogenes if they reduce the expression of tumor suppressor genes or as tumor suppressors if they reduce the expression of oncogenes. Moreover, the same miRNAs can have a dual function, having the ability to bind to different mRNA molecules [9]. MiRNAs are present in stable forms in body fluids, such as plasma or serum, so their expression profiles are tightly related to the pathological conditions inside the cells [10, 11].

This study is focused on miRNA-17-5p, miR-NA-93--5p, miRNA-320a, miRNA-519d-3p, miR-NA-526b-3p, and miRNA-5590-3p, which according to the reviewed literature, are associated with inflammation and carcinogenesis. MiRNA-17-5p was up-regulated in pancreatic adenocarcinoma and directly targeted retinoblastoma-like protein 2 (RBL2). High levels of miR-17-5p and low levels of RBL2 protein are associated with poor prognosis [12]. The summary of molecular targets for miRNAs is in Table 1 [12–25]. Moreover, miRNA-93-5p is involved in gemcitabine resistance in pancreatic cancer via targeting the PTEN-mediated PI3K/Akt signaling pathway [13]. There is an indication that miRNA-320a takes part in promoting 5-fluorouracil (5-FU) resistance of human pancreatic cancer cells by targeting the programmed cell death 4 (PDCD4) transcript and is involved in proliferation, invasion, metastasis, drug-resistance characteristics, and the epithelial-to-mesenchymal transition of pancreatic cancer [14]. Moreover, the expression of miR-320a is considered a predictive marker for chemotherapy in pancreatic cancer patients [14]. The miRNA-519d-3p is a suppressor molecule whose downregulation in pancreatic cancer was observed with the simultaneously high level of ribosomal protein S15a (RPS15A), a gene that regulates expression of β-catenin and activity of the Wnt signaling pathway [15] Up-regulation of miRNA-519d-3p could suppress proliferation of pancreatic cancer cells and activity of Wnt/β-catenin, imitating the impact of *RPS15A* silencing [15]. MiRNA-526b-3p is considered a tumor suppressor. MiRNA-526b-3p directly targets the 3'UTR (untranslated region) of E2F transcription factor 1 (E2F1), decreasing its expression. Overexpression of miRNA-526b-3p inhibited the proliferation of CRC cells by reducing the level of E2F1 [16]. In glioma, miRNA-526b-3p regulates the tumor process through WEE1 (WEE1 G2 checkpoint kinase), and it is reported as a prognostic factor for this neoplasm [17]. MiRNA-5590 is considered a tumor suppressor molecule that prevents excessive cell proliferation and migration; its importance has been evaluated in human gastric cancer and breast cancer [18, 19].

Table 1. Summarized table of molecular targets for miRNAs

Molecule	Role	Target genes	Citation
miR-17-5p	Oncogene	*RBL2*	[12]
miR-93-5p	Oncogene	*MDR1, PTEN, CDKN1A*	[13, 20]
miR-320a	Oncogene	*PDCD4*	[14]
miR-519d-3p	Tumor suppressor	*RPS15A, BCL6, CCND1, BCL-W, HIF-1a*	[15, 21–25]
miR-526b-3p	Tumor suppressor	*E2F1, WEE1*	[16, 17]
miR-5590	Tumor suppressor	*TGFβ-R1, TGFβ-R2, SMAD3, SMAD4*	[18, 19]

In this pilot study, we have examined the expression of the above-mentioned miRNAs in the plasma of CP, PDAC, and CRC patients and correlated them with available clinical and demographic data and with markers of carcinogenesis: CA19-9 and carcinoembryonic antigen (CEA).

Our study aimed to investigate the potential of selected molecules as diagnostic biomarkers. Additionally, we checked whether the examination of miRNA expression could help differentiate between CP and PDAC.

Materials and methods

Studied group

The study was approved by the Research Ethics Committee of the Medical University of Lublin (approval no. KE 0254-/54/2015) and conducted in conformity with the Declaration of Helsinki.

The study of plasma miRNA expression was performed in 88 patients. Blood samples were taken at the moment of diagnosis. The study population included 40 (45%) patients with chronic pancreatitis, 20 (23%) patients with pancreatic cancer (PC), and 28 (32%) patients with colorectal cancer (CRC). Fifty-nine (67%) male and 29 (33%) female patients were in the examined group [median age and standard deviations (SD): 63.5 ± 16.2 years, range 27–96 years]. The clinical and demographic data are presented in Table 2. The control group consisted of 31 healthy participants (median age and SD: 45 ± 11.8 years, range 29–67 years). The control group did not differ significantly in terms of age and sex from the examined group.

MicroRNAs isolation

Blood was collected in EDTA (ethylenediaminetetraacetic acid) tubes and then centrifuged (2000 × g, for 10 min.) to obtain plasma. Plasma was stored at –80°C until miRNA isolation.

Isolation of total RNA with miRNAs fraction from plasma was performed using miRNeasy Serum/Plasma Kit (Qiagen, Germany). The amount and purity of RNA were assessed using an Eppendorf BioPhotometer (Eppendorf, Germany). RNA was stored at –80°C until the reverse transcription reaction was performed.

Reverse transcription reaction

The TaqMan™ Advanced miRNA cDNA Synthesis Kit (Applied Biosystems, USA) was used to transcribe the miRNAs into complementary DNA (cDNA) according to the manufacturer's instructions. RT (Reverse transcription) was performed in a TPersonal Biometra thermocycler (Analytik-Jena Company, Germany). cDNA was stored at –20°C until quantitative polymerase chain reaction (qPCR) was performed.

Quantitative polymerase chain reaction

The expression of six microRNAs, which are attributed to properties of oncogenes or tumor suppressors (miRNA-17-5p, miRNA-93-5p, miRNA-320a-5p, miRNA-519d-3p, miRNA-526b-3p, miRNA-5590-3p), was assessed. Expression was examined by the qPCR method on the Illumina Eco (Illumina Inc, USA) device. The 20 microliter PCR mix for assessing miRNAs expression consisted of 10 μL TaqMan Fast Advanced Master Mix (Applied Biosystems, USA), 1 μL TaqMan Advanced miRNA Assay (separate reaction for each miRNA), 4 μL RNase-free water and 5 μL cDNA. Quantitative polymerase chain reaction was carried out under the following conditions: 95°C for 30 sec. and then 40 cycles: 95°C for 3 sec. and 62°C for 30 sec. miRNA-191-5p and cel-miR-39-3p were used as an internal control and spike-in control, respectively. Commercial sets of TaqMan primers and probes were used for each of the microRNAs and the internal control (Applied Biosystems, USA)

The $2^{-\Delta Ct}$ method was used for the calculation of the expression.

Statistical analysis

Statistical analysis was performed using Statistica 13 software (Tibco Software, USA). The Mann-Whitney U-test was used to assess the differences in expression of particular miRNAs between individual groups. Receiver operating characteristic (ROC) curves with area under the curve (AUC) analyzes were used to assess the diagnostic utility of miRNAs in distinguishing patients from healthy participants, as well as CP and PTAC patients. A p-value below 0.05 was considered significant.

Results

Comparison of microRNA expression in patients and healthy donors

MiRNA-17 expression was higher in patients with colorectal cancer compared to healthy participants ($p = 0.05$). Moreover, significantly higher expression of miRNA-93 was observed in patients with pancreatic cancer and colorectal cancer compared to healthy individuals ($p = 0.02$ and $p = 0.005$, respectively). Further, significantly lower expression of microRNA-519 was found in chronic pancreatitis and pancreatic cancer compared to healthy subjects ($p = 0.01$ and $p = 0.02$, respectively) (Fig. 1).

MiRNAs expression in patients

Significantly higher expression of miRNA-93 was observed in patients with CP who had a higher concentration of CA-19-9 compared to patients with a low level or unknown status of this marker ($p = 0.03$). Significantly lower expression of miRNA-519 was found in

Table 2.Clinical and demographic data of the patients included in the study

Features, n = 88 (100%)	CP (n = 40)	PDAC (n = 20)	CRC (28)
Age	Median age: 56 years (SD = 14.0, range: 27–87 years)	Median age: 64 years (SD = 13.3, range: 37–96 years)	Median age: 78 years (SD = 14.8, range: 40–91 years)
Age below the median; n = 43 (49%)	20 (50%)	9 (45)	14 (50%)
Age above the median; n = 45 (51%)	20 (50%)	11 (55)	14 (50%)
Sex			
Male; n = 59 (67%)	31 (77.5%)	10 (50%)	18 (64%)
Female; n = 29 (33%)	9 (22.5%)	10 (50%)	10 (36%)
Diabetes			
No; n = 69 (78%)	29 (72.5)	13 (65%)	27 (96%)
Yes; n = 19 (22%)	11 (27.5)	7 (35%)	1 (4%)
Acute pancreatitis in the past			
No; n = 71 (81%)	24 (60%)	19 (95%)	28 (100%)
Yes; n = 17 (19%)	16 (40%)	1 (5%)	0 (0%)
Metabolic syndrome			
No; n = 85 (96.5%)	39 (97.5)	20 (100%)	26 (93%)
Yes; n = 3 (3.5%)	1 (2.5)	0 (0%)	2 (7%)
Diet			
Light diet; n = 38 (43%)	13 (32.5%)	9 (45%)	16 (57%)
Does not follow the diet; n = 16 (18%)	13 (32.5)	3 (15%)	0 (0%)
Diabetic; n = 15 (17%)	7 (17.5%)	4 (20%)	4 (14%)
Fat-free and peptic ulcer diet; n = 2 (2%)	1 (2.5%)	0 (0%)	1 (4%)
No data; n = 17 (19%)	6 (15%)	4 (20%)	7 (25%)
Exposure to carcinogens			
No; n = 49 (56%)	12 (30%)	12 (60%)	25 (89%)
Yes (smoking, alcohol); n = 39 (44%)	28 (70%)	8 (40%)	3 (11%)
CEA			
< 4 U/mL; n = 63 (72%)	38 (95%)	9 (45%)	16 (57%)
≥ 4 U/mL; n = 15 (17%)	1 (2.5%)	5 (25%)	9 (32%)
No data; n = 10 (11%)	1 (2.5%)	6 (30%)	3 (11%)
CA-19-9			
< 37 U/mL; n = 28 (32%)	24 (60%)	4 (20%)	0 (0%)
≥ 37 U/mL; n = 28 (32%)	10 (25%)	15 (75%)	3 (11%)
No data; n = 32 (36%)	6 (15%)	1 (5%)	25 (89%)

CP — chronic pancreatitis; PDAC — pancreatic ductal adenocarcinoma; CRC — colorectal cancer; CEA — carcinoembryonic antigen

patients with chronic pancreatitis who were diagnosed with diabetes compared to patients without this disease (p = 0.02). Moreover, significantly higher expression of miRNA-320 was noticed in female in comparison to male patients with chronic pancreatitis (p = 0.004) (Fig. 2). No differences were found in the relative expression of the examined miRNAs between CP and PDAC patients.

The diagnostic value of miRNAs expression assessment

We found three molecules that differentiated CP, PC, and CRC from healthy subjects.

Examination of miRNA-519 expression distinguished patients with chronic pancreatitis from healthy volunteers with sensitivity and specificity of the diagnostic test at 60% and 80%, respectively [AUC = 0.68; 95% confidence interval (CI) 0.55–0.80; p = 0.006] (Fig. 3A).

Examination of miRNA-93 and miRNA-519 expression distinguished pancreatic cancer patients from healthy participants. The sensitivity and specificity of the diagnostic test for assessment of miRNA-93 expression were 60% and 77%, respectively (AUC = 0.69; 95% CI 0.53–0.85; p = 0.002). While the sensitivity and specificity of the diagnostic test for miRNA-519 were 59% and 79% (AUC = 0.69; 95% CI 0.53–0.85; p = 0.002) (Fig. 3B).

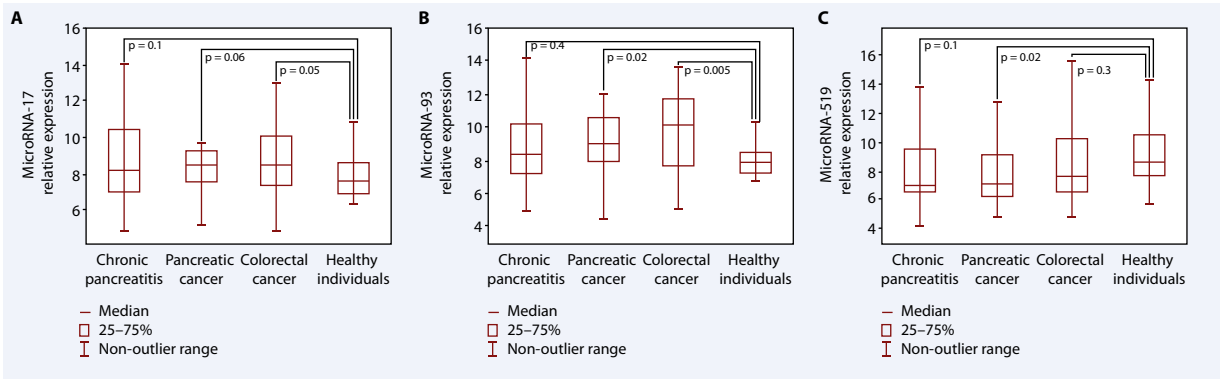

Figure 1. Comparison of the expression of selected miRNAs in patients with chronic pancreatitis (CP), pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC), and healthy volunteers

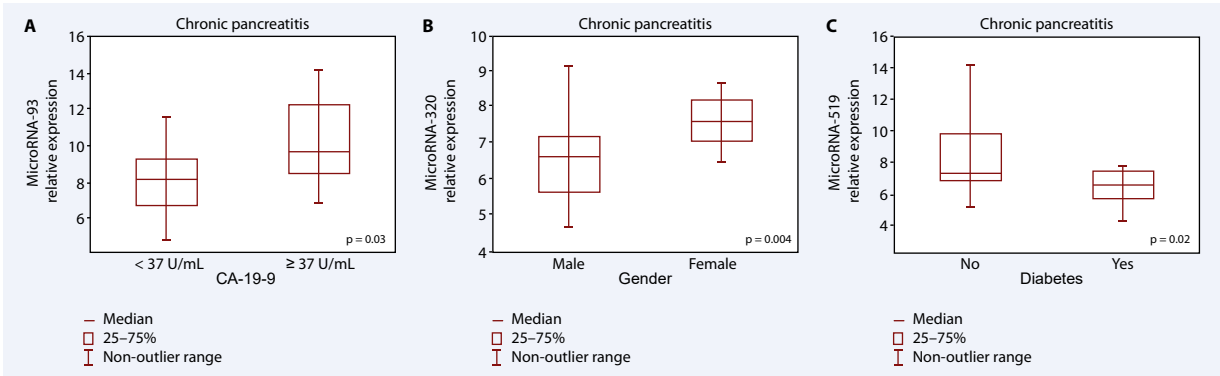

Figure 2. Expression of selected microRNAs in patients with chronic pancreatitis (CP) depending on CA 19-9 concentration, sex, and diabetes coexistence

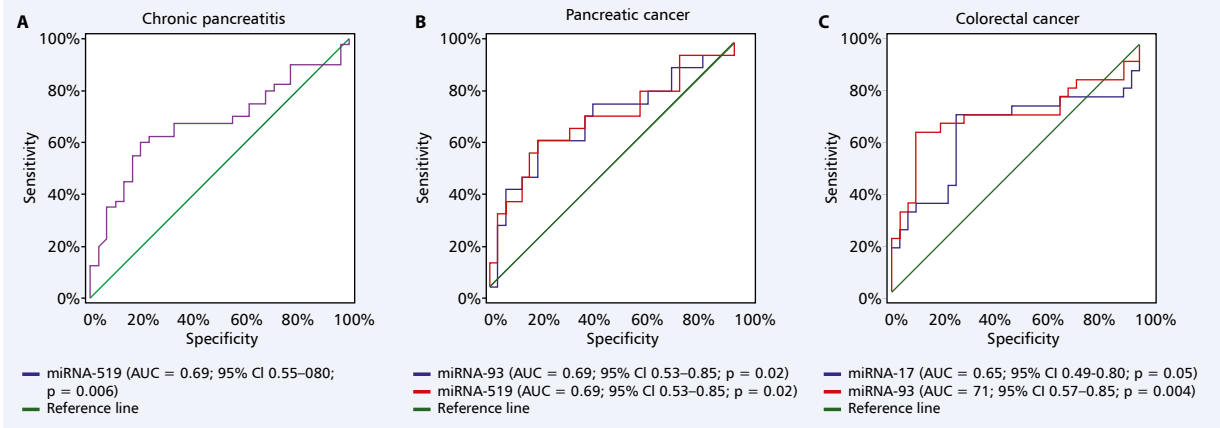

Figure 3. Sensitivity of the tests assessing the expression of selected miRNAs in distinguishing patients with chronic pancreatitis (CP), pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC) from healthy participants; AUC — area under the curve; CI — confidence interval

Examination of miRNA-17 and miRNA-93 expression distinguished patients with colorectal cancer from healthy participants. The sensitivity and specificity of the diagnostic test for examination of miRNA-17 expression were 78% and 50% (AUC = 0.65; 95% CI 0.49–0.80; p = 0.05). Test for miRNA-93 expression had 78% sensitivity and 80% specificity (AUC = 0.71; 95% CI 0.57–0.85; p = 0.004) (Fig. 3C).

Discussion

Despite advancement of research into early detection of malignant neoplasms, many cancers are still detected too late, especially pancreatic cancer, which is characterized by an aggressive course and a poor prognosis. Another problem is that the image on CT (computed tomography) or MRI (magnetic resonance imaging) is similar in pancreatic cancer and CP patients, so there is an urgent need to find markers allowing for differentiation of these two diseases. Nowadays, CA 19-9 is believed to be a blood marker in the early detection of PDAC, but on the other hand, it has a reduced diagnostic value because of false positive and false negative results [26]. This means that CA 19-9 level is elevated not only in PDAC but also in the biliary tract, stomach, colorectal, lung, or thyroid tumors and also in non-malignant pathologies, including pancreatitis, diabetes mellitus, as well as other pulmonary, thyroidal, and gynecologic diseases [27]. Moreover, another limitation of CA 19-9 examination is the fact that as a sialylated Lewis blood group antigen, also CA 19-9 is not detected in people who lack the expression of fucosyltransferase, an enzyme required for the production of both CA 19-9 and Lewis antigen [28]. The above problems do not allow the detection of PDAC in early stages and prevent effective surgical treatment [28].

We have much greater possibilities in the early detection of colorectal cancer thanks to the wide availability of screening tests, including colonoscopy. However, due to the reluctance (aversion) of patients to this examination, the need for tiring preparation and high costs, markers are necessary to facilitate identification of the best candidates for this study. The CEA tumor marker has fallen short of expectations and is not recommended for screening. Also in our study, the majority of CRC patients had normal or slightly raised CEA level at the moment of diagnosis.

Aberrant miRNA expression profiles have been studied in many types of cancers, including PDAC and colorectal cancer [29]. MiRNAs may be interesting blood-based biomarkers in clinical practice because they are stable in circulation, not degraded by endogenous RNases, non-invasive, and simple to collect [30]. Chronic inflammation regulates carcinogenesis on different levels, starting from tumor initiation, through proliferation and progression, ending up in metastasis; miRNAs are involved in this process [31]. Depending on the type of tumor and immune cells involved in this process, mediators produced by inflammatory cells increase mutagenesis and activate epigenetic machinery, including histone modifications, long non-coding RNA and miRNAs that modulate gene expression and promotor gene methylation [32]. Accumulating evidence indicates that miRNAs are frequently dysregulated in human cancers, and alterations of miRNAs expression in CRC have been well documented [33].

As miRNAs are mediators in carcinogenesis and inflammation, we have selected a group of miRNAs potentially involved in CRC, PDAC, and CP pathophysiology. We chose also some miRNAs known for having a potential diagnostic and prognostic role in patients with other cancers, especially lung cancer. In the next part of the discussion, we will look at those miRNAs that were associated with CP, PDAC, or CRC in our study: miRNA-17-5p, miRNA-93-5p, and miRNA-519d-3p.

The examination of the miRNA-93-5p molecule appears to have a diagnostic, predictive, and therapeutic potential. The test based on the evaluation of the level of this molecule in the serum or plasma was very promising; however, some limitations of this microRNA should be pointed out. In our study, high expression of miRNA-93-5p occurred in colorectal-cancer and pancreatic-cancer patients, with no significant difference between these cancers. That is, this molecule is not tumor-specific and, arguably, cannot be used as a stand-alone diagnostic or prognostic/predictive factor. However, it can be a valuable ancillary parameter for cancer screening, early cancer diagnosis, or the likelihood of resistance to treatment. Shao et al. indicated that a test based on a combined analysis of the miR-93-5p and miR-18a expression in serum (miR-93-5p+miR--18a marker) has a better value potential for diagnosis and prognosis in non-small cell lung cancer (NSCLC) patients than the examination of single markers [34]. Likewise, Vila-Navarro et al. indicated that multiple miRNAs assessed simultaneously in one test provided much better information (in terms of sensitivity and specificity) in the identification of PDAC. Moreover, they showed that CA19.9 increased the diagnostic potential of test-examined miRNAs signatures. The test combining miRNAs and CA19.9 (miR-33a-3p+miR--320a+CA19.9) achieved an AUC of 0.95 (93% sensitivity and 85% specificity) [35]. In our study, we observed significantly higher expression of the miR-93 molecule in the group of patients suffering from chronic pancreatitis, with a concentration of this marker above 37 U/mL. Nevertheless, we did not observe such a relationship in pancreatic cancer patients, and we found no differences in the expression of this miRNA between CP and PDAC. We think it is worthwhile to expand our study to an enlarged group of CP and PDAC patients and include protein tumor markers and other microRNAs that have the possibility of differentiating these two diseases.

The miR-93-5p molecule is considered to be oncogenic, whereas in our study we also observed a significant decrease in expression of the tumor suppressor miR-519d-3p in patients with both chronic pancreatitis and pancreatic cancer. Furthermore, we found that the expression of this molecule is significantly reduced

in patients with chronic pancreatitis who were also diagnosed with diabetes. We tentatively suggest that this microRNA could be disease-tissue-specific. However, there is limited research on pancreatic diseases involving this molecule. Table 3 [20–25, 34–42] contains information on the miRNA-17-5p, miRNA-93, and miRNA-519d-3p molecules and their role in cancer in relation to the results obtained in this study.

Table 3. Description of miRNA-17-5p, miRNA-93, and miRNA-519d-3p roles in cancer in relation to the results obtained in this study

miRNA	Characteristic	Source
miRNA-17-5p	Expression is higher in patients with colorectal cancer compared to healthy participants with sensitivity and specificity 78% and 50%, respectively	The study presented here
	Cancer patients with high expression of miR-17-5p have a worse prognosis than those with low expression. This molecule may be involved in the progression of lymphatic metastasis and vein invasion in cancer	Kong et al. [36]
	Metastasis suppression function	Fan et al. [37]
miRNA-93	Distinguished patients with colorectal cancer from healthy donors with 78% sensitivity and 80% specificity	The study presented here
	Distinguished patients with PC from healthy volunteers (higher expression in PC) with 60% and 77% of sensitivity and specificity, respectively	The study presented here
	High circulating miR-93 expression could discriminate between pancreatic cancer patients and healthy people, with AUC = 0.80	Vila-Navarro et al. [35]
	The 3-year survival rate of NSCLC patients is significantly lower in the group of patients with low miR-93-5p serum expression than in the group of patients with high expression of this molecule (log-rank: p = 0.0442); has a diagnostic potential with AUC = 0.7926	Shao et al. [34]
	An increased expression of urinary exosomes (UEs) derived miRNA-93 has a diagnostic potential to discriminate BC patients from the healthy people with AUC = 0.838; high miR-93-5p serum level is significantly associated with early BC recurrence	Lin et al. [38]
	High serum level is a potential prognostic factor for the risk of early disease recurrence in CRLM; expression is significantly higher in CRLM in comparison to the non-metastatic liver tissue	Despotović et al. [39]
	An exosomal cargo responsible for the pro-tumorigenic effects of cancer-associated fibroblasts in colorectal cancer. Cancer-associated fibroblast exosomes contained more miR-93-5p than normal fibroblast exosomes, which increased the proliferation of CRC cells and protected them from radiation-induced apoptosis	Chen et al. [40]
	Is elevated in drug-resistant CRC cells, and downregulation of miR-93-5p expression results in increased sensitivity to chemotherapy; inhibition of miR-93-5p is found to downregulate MDR1 (ATP binding cassette subfamily B member 1, ABCB1) expression, increase intracellular chemotherapeutic concentration, and increase the percentage of cells in the G1 cycle phase by upregulating Cyclin Dependent Kinase Inhibitor 1A (CDKN1A) gene and protein expression	Wang et al. [20]
miRNA-519d-3p	Expression distinguishes patients with chronic pancreatitis from healthy volunteers with sensitivity and specificity of 60% and 80%, respectively while the sensitivity and specificity of this test in distinguishing pancreatic cancer patients from healthy participants is 59% and 79%, respectively	The study presented here
	Functions as a tumor suppressor by targeting and downregulating the expression of B-Cell Lymphoma 6 Protein (BCL6)	Li et al. [21]
	Expression significantly decreased in glioma tissues; regulation of B-Cell Lymphoma 1 Protein (CCND1)	Ma and Li [22], Zhang and Hong [23]
	In OSCC tissues, downregulating miR-519d-3p expression correlated with a higher tumor grade, and upregulating miR-519d-3p expression inhibited OSCC cells viability and proliferation as well as increased cells in G0/G1 cell cycle	Zhang and Hong [23]
	Plasma expression is significantly decreased in NSCLC patients compared to healthy individuals; molecular targets of this molecule: BCL2-like protein 2 (BCL-W) and hypoxia-inducible factor 1 subunit alpha (HIF-1α): miRNA-519 and expression of BCL-W and HIF-1 α mRNA showed an inverse correlation in NSCLC	Choi et al. [24]
	HIF-1A mRNA is negatively correlated with the miR-519d-3p levels in human PDAC tissue samples; miR-519d-3p negatively regulated ribosomal protein S15a (RPS15A) expression in pancreatic cancer cells	Sun et al. [25]
	Expression is significantly decreased in pancreatic cancer tissues, which is involved in the Wnt /β-catenin signaling pathway	Liang et al. [41]
	Levels in pancreatic cancer cells were reduced following hypoxia; transfection with miR-519 mimics inhibited pancreatic cancer cells' invasiveness and induced apoptosis under hypoxic conditions; programmed death ligand 1 (PD-L1) as a target of miR-519 and rescued the miR-519 mimic-attenuated tumorigenesis of pancreatic cancer cells under hypoxic conditions; treatment with miR-519 significantly suppressed the tumor growth of pancreatic cancer cells	Nong et al. [42]

AUC — area under the curve; PC — pancreatic cancer; NSCLC — non-small cell lung cancer; BC — bladder cancer; CRLM — colorectal cancer with liver metastasis; CRC — colorectal cancer; OSCC — oral squamous cell carcinoma; PDAC — pancreatic ductal adenocarcinoma

There is no evidence of the impact of circulating miRNA-519d-3p as a biomarker in chronic pancreatitis. We showed that examination of miRNA-519 expression distinguished patients with chronic pancreatitis from healthy volunteers with sensitivity and specificity of 60% and 80%, respectively, while the sensitivity and specificity of this test in distinguishing pancreatic cancer patients from healthy participants were 59% and 79%, respectively. However, this finding must be confirmed and validated in an independent enlarged study group.

Our studies have some limitations, such as small study groups or lack of data on the stage or localization of possible metastases. However, there may be strong indications to extend the research to an enlarged group of patients and to conduct it using biological tests that would indicate the target transcripts for the studied miRNA molecules.

Conclusions

Our study indicated that microRNA-93 has diagnostic potential in colorectal and pancreatic cancers, but literature data indicated that it cannot be a stand-alone diagnostic/predictive factor. In the case of miRNA-519d-3p, due to limited literature data on serum/plasma studies in pancreatic cancer or chronic pancreatitis, we could draw conclusions based on our own studies, which suggested that this molecule probably has a suppressor function and its expression can be a supportive factor for the diagnosis of PDAC or CP. However, it does not distinguish between these two diseases.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Sacituzumab govitecan — a new therapy for patients with triple-negative breast cancer

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ABSTRACT

Treatment outcomes in patients with metastatic triple-negative breast cancer (TNBC) have not improved significantly for many years. Modern treatments, including immune therapy and poly ADP-ribose polymerase (PARP) inhibitors, are available for a select group of TNBC patients. In many cases, classic chemotherapy remains the treatment of choice, which produces unsatisfactory response rates. The poor prognosis of patients with metastatic TNBC justifies intensive research on new drugs for this group of patients, including attempts to use conjugates. This article discusses the reports on sacituzumab govitecan (SG), which is composed of a monoclonal antibody targeting trophoblast-cell surface antigen 2 (Trop-2) expressed on many TNBC cells and linked to a payload (SN-38), the active metabolite of irinotecan. The structure and mechanism of action of this conjugate are presented. The available results of clinical trials with SG in breast cancer patients are summarized, including the results of the ASCENT registration study, which showed a significant improvement in the median progression-free survival, as well as overall survival, compared to classic chemotherapy in patients previously treated with advanced TNBC. The most common side effects of the drug are discussed, indicating principles of primary and secondary prophylaxis that allow for effective management of possible complications. Directions for further research in breast cancer patients on this very promising conjugate were also indicated.

Key words: sacituzumab govitecan, triple-negative breast cancer, conjugate, Trop-2

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Introduction

Treatment of patients with triple-negative breast cancer (TNBC) remains a challenge for oncologists. For cancers with either estrogen receptor (ER) expression or human epidermal growth factor receptor 2 (HER2) overexpression, modern therapies have been developed which allowed for a significant extension of median overall survival (OS) in patients with distant metastases [1, 2]. TNBC is associated with a much worse prognosis. The introduction of innovative drugs (e.g. immunotherapy) made it possible to achieve OS of 25 months in breast cancer patients with expression of programmed death ligand 1 (PD-L1) [3, 4]. While chemotherapy alone is still a standard of care in the remaining patients, its effectiveness is limited [5, 6]. The median OS in patients with metastatic TNBC is up to 16–18 months [3, 4, 7]. The above data indicate that TNBC is currently the most aggressive breast cancer subtype. Intensive research is being conducted on new therapies that would improve the prognosis. As a result, new drugs (including conjugates) are being developed. One of the very promising ones is sacituzumab govitecan (SG).

This article discusses the structure and mechanism of action of SG, summarizes the results of available studies on using the drug in breast cancer patients, and presents the profile of side effects and practical guides for management during SG administration.

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Structure and mechanism of action of sacituzumab govitecan

Sacituzumab govitecan is a conjugate containing the monoclonal antibody sacituzumab that binds to the trophoblast-cell surface antigen 2 (Trop-2) on the surface of cancer cells, SN-38 active loading (govitecan), and a linker [8]. Approximately 7–8 molecules of SN-38 are attached to each antibody molecule (mean 7.6) (Fig. 1). SN-38 is a cytotoxic metabolite of irinotecan that inhibits topoisomerase I. It is 100–1000 times stronger than irinotecan. After SG administration, the monoclonal antibody binds to Trop-2 present on the cancer cell surface, then the receptor-conjugate complex is internalized, thanks to which SN-38 enters the cancer cells. SN-38 is released from the lysosomes and enters the cell nucleus, where it damages DNA by inhibiting topoisomerase I. The linker between antibody and payload has intermediate stability, which allows for the slow release of SN-38. Unbound SN-38 can cross cell membranes and reach and destroy the tumor microenvironment. This is due to the release of SN-38 from the tumor cells after internalization and splitting of SN-38 by linker hydrolysis before the conjugate internalization. This makes it possible to destroy Trop-2 negative cells (bystander effect) [9].

Trop-2 is a cell-surface glycoprotein, reported to be overexpressed in breast cancer, lung cancer, gastric cancer, colorectal cancer, pancreatic cancer, prostate cancer, cervical cancer, ovarian cancer, as well as head and neck cancers [9]. Trop-2 overexpression in cancer cells stimulates their growth and metastasis through promotion of cell proliferation and motility. Trop-2 is also involved in the process known as epithelial-mesenchymal transition (EMT) [10]. There are limited studies on Trop-2 prognostic value in breast cancer. According to the current evidence, patients with high Trop-2 expression have more aggressive disease and a worse prognosis [11]. Importantly, Trop-2 expression is found in the vast majority of TNBCs, with a positive result rate of over 85% [9, 12, 13]. The above reports contributed to the attempts to use Trop-2 as a potentially attractive target of anti-cancer therapy.

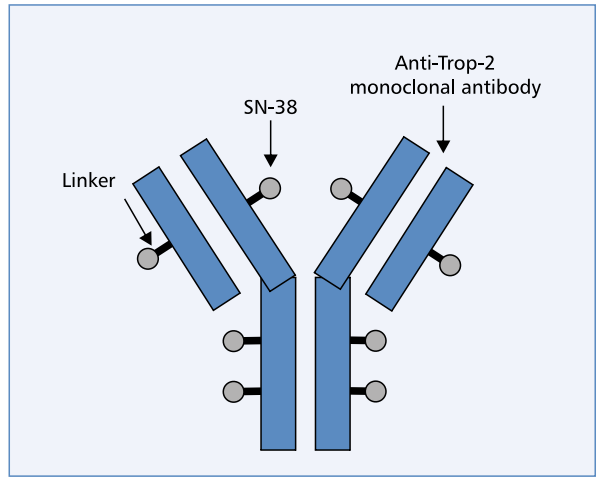

Figure 1. Structure of govitecan sacituzumab; Trop-2 — trophoblast-cell surface antigen 2

Results of studies with sacituzumab govitecan in patients with triple-negative breast cancer

Phase I/II study

The first reports on the use of SG come from a phase-I trial, in which the treatment was used in 25 patients with various cancers (including 4 patients with TNBC). A clinical benefit was found in half of them [14]. The recommended SG dose for further studies was determined at 10 mg/kg body weight (BW).

Subsequently, the phase-I/II IMMU-132-01 basket trial was designed, which enrolled patients with various cancers (including patients previously receiving at least two lines of treatment for metastatic TNBCs). Patients were treated with SG administered intravenously on days 1 and 8 of the cycle, every 21 days, at the above-mentioned dose of 10 mg/kg BW. The general condition of the patients was good. The preliminary results of the study were published in 2017 [12]. After analyzing 69 patients with TNBC, the objective response rate (ORR) was 30%, and the clinical benefit rate (CBR) was 46%. The median progression-free survival (PFS) was 6 months, and the median OS was 16.6 months.

The final analysis of the phase-II study included data from 108 TNBC patients who underwent SG therapy (usually after 3 previous treatment lines; range 2–10) [15]. The vast majority of patients had previously received taxoids (98%) and anthracyclines (86%). Seventeen percent of patients had previously undergone immunotherapy. After 10 months of follow-up (median) ORR was 33%, CBR 45%, median PFS 5.5 months, and median OS 13.0 months.

ASCENT study

The obtained results contributed to the design of the phase-III clinical study ASCENT [13]. This open-label, randomized trial enrolled 529 patients with metastatic or inoperable locally advanced TNBC. Previously, at least 2 lines of systemic treatment were used (one of which could have been perioperative chemotherapy provided that relapse occurred within 12 months of completion). The study involved 61 patients with sta-

Table 1. Summary of the results of studies with sacituzumab govitecan in breast cancer patients

Indication	Study	Treatment schedule	Number of pts. (N)	ORR	CBR	Median PFS (months)	Median OS (months)
TNBC	IMMU-132-01 [15]	SG	108	33% (3% CR and 30% PR)	45%	5.5	13
	ASCENT (IMMU-132-05) [13]	SG *vs.* chemotherapy	235 *vs.* 233	35% (4% CR and 31% PR) *vs.* 5% (1% CR and 4% PR)	45% *vs.* 9%	5.6 *vs.* 1.7; HR = 0.41	12.1 *vs.* 6.7; HR = 0.48
ER+/HER2-	IMMU-132-01 [22]	SG	54	32%	44%	5.5	12

CBR — clinical benefit rate; CR — complete response; ER — estrogen receptor; HR — hazard ratio; ORR — objective response rate; OS — overall survival; PFS — progression—free survival; PR — partial response; SG — sacituzumab govitecan; TNBC — triple-negative breast cancer

ble brain metastases. The study compared SG with single-drug chemotherapy (oral capecitabine at a dose of 2000–2500 mg/m^2 daily on days 1–14 every 3 weeks), or intravenous eribulin at a dose of 1.23–1.4 mg/m^2 on days 1 and 8 of the cycle every 21 days, or intravenous gemcitabine at a dose of 800–1000 mg/m^2 on day 1, 8, and 15 of the cycle every 28 days, or vinorelbine intravenously at a dose of 25 mg/m^2 every week) chosen by the investigator. The dosing of SG was standard (intravenous infusions of 10 mg/kg BW on days 1 and 8 of the cycle every 21 days). Treatment was continued until progression or unacceptable toxicity.

The primary endpoint of the study was median PFS in patients without brain metastases — the analysis included 235 patients in the experimental arm and 233 patients in the control group (468 patients in total). Secondary endpoints were OS in the cohort without brain metastases, PFS and OS in the overall population, ORR, safety, and quality of life.

The performance status according to the Eastern Cooperative Oncology Group scale (ECOG PS) was good (0-1). All patients had previously received taxoids, most of them also had anthracyclines (82%), and more than half had carboplatin (66%); 7% of patients had previously received therapy with PARP inhibitors, and 27% received immunotherapy.

After a median follow-up of 17.7 months, an improvement was achieved in the SG group. Median PFS in the population without brain metastasis, the primary endpoint, was 5.6 months in the SG arm and 1.7 months in the control arm [hazard ratio (HR) = 0.41; 95% confidence interval (CI): 0.32–0.52; p <0.001]. PFS advantage in the SG arm was observed in all predefined subgroups, including patients ≥ 65 years of age, with more than 3 prior treatment lines, and after immunotherapy. The median OS was 12.1 months in the SG group and 6.7 months in patients undergoing chemotherapy (HR = 0.48; 95% CI 0.38–0.59; p <0.001). The results of OS subgroup analyses were constantly more favorable for SG compared to chemotherapy. There was also a significant improvement in ORR in the experimental arm (35% compared with 5% in patients undergoing standard chemotherapy). Similarly, CBR was greater in the SG group (45%) than in the control arm (9%).

Patients with brain metastases, most of whom had previously received 5 treatment lines, were analyzed separately [16]. There was numerically higher median PFS in the group treated with SG compared to chemotherapy (2.8 *vs.* 1.6 months) and similar results in terms of OS (6.8 and 7.5 months, respectively). On the other hand, ORR in both groups was 0% and 3%, and CBR was 9.4% and 3.4%, respectively. However, it should be highlighted that the analyzed subgroup with brain metastases was small, and the results regarding the effectiveness of the treatment require further studies.

The results of SG studies in breast cancer patients are summarized in Table 1.

Predictive biomarkers for sacituzumab govitecan efficacy

In the case of targeted therapies, response biomarkers are sought to more accurately qualify patients who have the best chance of obtaining benefits from the therapy. The Trop-2 expression seems to be the most promising biomarker of SG response [17]. In the above-mentioned study, the intensity of Trop-2 expression was determined by immunohistochemistry (IHC) in 290 patients, and three groups were distinguished, taking into account the percentage of stained cells and its intensity (H-score from 0 to 300). The most numerous was the group with high Trop-2 expression (H-score > 200–300) (54% of patients), while the group with intermediate expression (H-score 100–200) and low Trop-2 expression 2 (H-score from 0 to < 100) included 26% and 20% of patients, respectively.

Patients in the experimental arm with high, moderate, and low Trop-2 expression had median PFS of 6.9 months, 5.6 months, and 2.7 months, respectively. On the other hand, median PFS in the control arm in respective groups was considerably lower (2.5, 2.2, and 1.6 months, respectively). Patients in the group treated with SG with enhanced Trop-2 expression had also

improved OS outcomes. Median OS was 14.2 months, 14.9 months, and 9.3 months in the subgroups with high, intermediate, and low Trop-2 expression, respectively, and 6.9 months, 6.9 months, and 7.6 months in the respective subgroups in the chemotherapy arm. A similar association between ORR and intensity of Trop-2 expression was observed in the SG-treated group. The ORR in the experimental group was 44% *vs.* 1% in the group with high Trop-2 expression, 38% *vs.* 11% in the group with intermediate expression, and 22% *vs.* 6% in the group with low Trop-2 expression as compared to the control arm.

The mutation status of the *BRCA1/2* genes was known in 292 patients in the ASCENT study, and *BRCA* mutation was found in 12% of the analyzed patients. However, the conducted analyses did not show any differences in treatment outcomes depending on *BRCA* gene mutation status. SG therapy was significantly better compared to standard chemotherapy [17].

The analysis presented above is the basis for further research on the *predictive* biomarkers for *SG* efficacy. Currently, patients are eligible for SG treatment regardless of Trop-2 expression status. Further studies may allow for limiting the group of patients qualified for treatment. The authors of the analysis indicated that the size of the group of patients with low Trop-2 expression was small, which does not allow for formulating unequivocal recommendations limiting the use of SG in these patients.

Side effects of sacituzumab govitecan

All patients in the aforementioned phase-I/II study experienced adverse effects, with 66% and 19% experiencing grade 3 and grade 4 adverse effects (AEs), respectively. The most common adverse reactions were nausea (67%), diarrhea (62%), fatigue (55%), neutropenia (64%), anemia (50%), and the most common grade 3 or higher (with a frequency > 10%) were neutropenia (26%) and anemia (11%). Febrile neutropenia was diagnosed in 10 patients (9%). Adverse events leading to treatment witholding occurred in 48 of 108 patients (44%); the most common cause was neutropenia. Three patients (3%) discontinued treatment due to side effects of therapy [15].

A similar toxicity profile was observed in patients treated in the ASCENT study [13]. The most common treatment-related AEs (TRAEs) of all grades were neutropenia (63% in the SG group *vs.* 43% in the chemotherapy group), diarrhea (59% *vs.* 12%), nausea (57% *vs.* 26%), alopecia (46% *vs.* 16%), fatigue (45% *vs.* 30%), and anemia (34% *vs.* 24%). The most common grade 3 TRAE was neutropenia (51% in SG group *vs.* 33% in the chemotherapy arm), followed by leukopenia (10% *vs.* 5%), diarrhea (10% *vs.* 1%), anemia (8% *vs.* 5%), and febrile neutropenia (6% *vs.* 2%).

An additional analysis was performed to assess the effectiveness of SG and treatment complications in elderly patients [18]. The treatment outcomes in patients aged 65 and older were found to be similar to those in the overall population while the incidence of complications was slightly higher, indicating the need for closer monitoring.

In the ASCENT study, granulocyte colony-stimulating factor (G-CSF) was used in 49% of patients receiving SG and 23% of patients receiving chemotherapy. The percentage of patients with dose reduction due to AEs was also similar (22% in the SG group *vs.* 26% in the chemotherapy group). It has been shown that reducing the SG dose did not translate into a decreased treatment effectiveness [19]. Adverse events leading to treatment discontinuation were rare and occurred in 12 patients (5%) in each group. There were 3 deaths due to adverse events in each study arm, but neither was associated with SG use [13].

Patients' quality of life during treatment with sacituzumab govitecan

In the ASCENT study, patients' quality of life was assessed before starting the treatment, before each cycle, and after treatment discontinuation with the use of the EORTC QLQ-C30 questionnaire [20]. The analysis included all participants with available baseline data and at least one assessment following treatment initiation. The quality of life of patients actively treated from the 2nd to the 6th cycle of therapy was compared.

The quality-of-life analysis included a total of 419 patients. At baseline, the quality-of-life scores did not differ between the study groups. It was found that quality of life in the SG arm was improved compared to chemotherapy in the following subscales: general health (0.7 *vs.* –3.4), physical functioning (1.3 *vs.* –4.4), and emotional functioning (3.3 *vs.* –0.5), additionally indicating lower intensity of fatigue (2.0 *vs.* 7.1), pain (–8.9 *vs.* –1.9), dyspnea (–3.8 *vs.* 4.0) and insomnia (–4.7 *vs.* 0.3). Among all the symptoms reported by patients in the SG group, worse results were noted only for diarrhea (14.1 *vs.* –1.3).

In conclusion, the quality of life was maintained or improved in the SG group. Diarrhea was more frequently reported by patients in the experimental arm; however, this did not translate into an overall assessment of health or functioning.

Recommended supportive care

Based on observations conducted during studies with SG, it is recommended that the first infusion of the drug should last 3 hours, and subsequent infusions

from 1 to 2 hours, provided that the earlier ones were well tolerated [21]. Premedication (including antipyretics, histamine type 1 and type 2 receptor blockers, or corticosteroids, e.g. 50 mg of hydrocortisone or its equivalent, administered orally or intravenously) is recommended in patients treated with SG. In addition, prophylaxis of nausea and vomiting should be given in the form of two or three antiemetics (e.g. dexamethasone with serotonin receptor antagonist or neurokinin 1 receptor antagonist).

A complete blood count should be monitored during the treatment, and SG should not be administered if the absolute neutrophil count is less than 1500/mm^3 on day 1 of the cycle or less than 1000/mm^3 on day 8 of the cycle. The time to neutropenia onset is usually 15 days from treatment initiation, with median duration of 8 days. In patients with severe neutropenia or febrile neutropenia, G-CSF administration may be necessary, with SG dose adjustment after resolution.

The time to diarrhea onset is usually 13 days from treatment initiation, with median duration of 8 days. In addition, SG should not be administered in the case of grade ≥ 3 diarrhea, and treatment could only be restarted after resolution to grade ≤ 1. After an infectious etiology has been ruled out, symptomatic treatment with loperamide, as well as fluids and electrolytes replacement should be started. In some patients who develop an excessive cholinergic response to SG treatment (e.g. in the form of stomach cramps, diarrhea, ptyalism), appropriate treatment (e.g. atropine) may be given as part of premedication before subsequent SG cycles.

SN-38 is metabolized via uridine *diphosphate glucuronosyltransferase* 1A1 (UGT1A1). Genetic variations of the *UGT1A1* gene (e.g. UGT1A1* 28 allele) lead to less UGT1A1 enzymatic activity. It has been observed that patients who are homozygous for the UGT1A1* 28 allele are potentially at greater risk of developing complications (including neutropenia, febrile neutropenia, and anemia). Approximately 20% of the black population, 10% of the white population, and 2% of the East Asian population are homozygous for the UGT1A1* 28 allele. Patients with lower UGT1A1 activity should be closely monitored for side effects. However, there are no indications for routine determining UGT1A1 activity in medical practice. The management of adverse effects, including recommended dose modification, is identical for all patients treated with SG [13, 21].

In addition, caution is required in all patients receiving SG with concomitant use of UGT1A1 inhibitors (e.g. ketoconazole or propofol) or inducers (e.g. carbamazepine or phenytoin), which may affect SN-38 activity.

Data on SG are summarized in Table 2.

Table 2. Summary of data for sacituzumab govitecan

Sacituzumab govitecan
Conjugate composed of anti-Trop2 monoclonal antibody combined with SN-38 (active metabolite of irinotecan — topoisomerase I inhibitor)
Dosage: 10 mg/kg body weight, intravenously on days 1 and 8, cycles every 21 days
Side effects: most common neutropenia, diarrhea, nausea, alopecia, weakness
Recommended primary prophylaxis of infusion reactions and nausea/vomiting, secondary prophylaxis in severe neutropenia
Symptomatic treatment of diarrhea: loperamide; in the case of severe early cholinergic symptoms, additionally atropine before subsequent infusions
Improvement or maintenance of quality of life in patients treated with SG compared with chemotherapy
Significant improvement in median PFS and OS as well as ORR and CBR rates
EMA registration: advanced or metastatic TNBC after prior treatment

CBR — clinical benefit rate; EMA — European Medicines Agency; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; SG — sacituzumab govitecan; TNBC — triple-negative breast cancer

Future perspectives

There are numerous clinical trials with SG in patients with TNBC, including preoperative treatment (the NeoSTAR study), adjuvant treatment in patients with residual disease (the SASCIA study in HER2-negative cancers), and palliative treatment [monotherapy or in combination with pembrolizumab (the Saci-IO study), atezolizumab, or talazoparib]. In addition, a clinical study for patients with brain metastases has been planned.

SG is also assessed in patients with ER+/HER2--breast cancer. The first data are from the phase-I/II IMMU-132-01 basket study, presented above [22]. Patients who previously received at least one line of hormone therapy and one line of chemotherapy due to metastatic breast cancer were eligible for the study. The results of 54 patients in whom SG was used at the recommended dose of 10 mg/kg BW on days 1 and 8 of the cycle every 21 days are already presented. All patients had previously received hormone therapy, 85% used taxoids, 67% anthracyclines, 65% capecitabine, 61% CDK 4/6 inhibitor, and 44% mTOR inhibitor. ORR was 32%, while CBR was 44%. Median PFS was 5.5 months and median OS was 12 months. The toxicity profile of SG was similar to that seen in the studies in TNBC patients. The most common grade 3 adverse reactions were neutropenia (50% of patients), anemia (11.1%), and diarrhea (7.4%). Two patients discontinued treatment due to adverse events. No deaths related to SG therapy have been reported.

Further clinical trials are currently ongoing in patients with ER+/HER2- breast cancer treated with SG in monotherapy compared with chemotherapy (the TROPiCS-02 study), as well as SG in combination with pembrolizumab (the Saci-IO HR+ study).

The results of the above-mentioned studies will allow us to determine the optimal setting in which SG should be used in breast cancer patients in a few years and possibly extend the current indications for using this promising drug.

Conclusions

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved SG as the first conjugate for the treatment of patients with advanced inoperable or metastatic TNBC who have been previously treated [21]. SG is made of an anti-Trop-2 antibody combined with SN-38 molecules (topoisomerase I inhibitor — the active metabolite of irinotecan). The pivotal ASCENT study showed a significantly greater benefit in terms of median PFS (5.6 months) and OS (12.1 months), as well as ORR (35%) and CBR (45%) with SG compared to standard chemotherapy [13]. Predictive factors for response to SG treatment are being sought, and preliminary observations indicate a promising role of Trop-2 expression. The most common side effects of SG are diarrhea and hematological complications (including neutropenia). The principles have been developed that allow for efficient management of complications [21]. The quality of life of patients in the studies was maintained or better in the SG group despite higher diarrhea incidence. Based on the results of the ASCENT study, SG is recommended for use in the 2nd line treatment in patients with metastatic TNBC [6].

There are multiple clinical trials on SG in patients with TNBC and ER+/HER2- breast cancer. The outcomes will provide a better understanding of indications for SG treatment.

Conflict of Interest

KP: Fees for consultations/lectures/training/clinical trials and fees for scientific congresses: Roche, Novartis, Eli Lilly, Pfizer, MSD, AstraZeneca, Gilead, Teva, Egis, and Vipharm.

AJG: Fees for consultations/lectures/training/clinical trials: AstraZeneca, Novartis, Roche, Gilead, Eli Lilly, Amgen, Pfizer, and MSD.

AN: Fees for consultations/lectures/training/fees for scientific congresses: Pfizer, Novartis, and Roche.

ZN: Fees for consultations/lectures/training/clinical trials: Roche.

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VIA MEDICA

REVIEW ARTICLE

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The role of anthracycline and pertuzumab in preoperative treatment of HER2-positive breast cancer

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ABSTRACT

Polychemotherapy combined with trastuzumab (T) or trastuzumab with pertuzumab (TP) is a standard preoperative systemic treatment in patients with HER2-positive breast cancer. In Poland T is reimbursed according to the Drug Prescription Program of Ministry of Health (MoH) for patients with primary breast tumors bigger than 1cm independently from nodal status, whereas TP is reimbursed for patients with tumors bigger than 2 cm with positive lymph node(s) or lack of hormonal receptors expression. The Drug Prescription Program does not indicate which polychemotherapy should be combined with anti-HER2 therapy. Therefore, one can choose between classical sequential treatment based on anthracycline and taxane combined with T or dual HER2 blockade (usually 4 × AC → 12 × paclitaxel/4 × docetaxel + T/TP), or docetaxel with carboplatin combined with trastuzumab (TCH) or with dual HER2 blockade (TCHP). According to the present guidelines of the National Comprehensive Cancer Network (NCCN), polychemotherapy without anthracycline is preferred, which is justified because of its lower toxicity, especially cardiotoxicity. Currently, a pathologically confirmed complete response (pCR) is usually the primary objective in clinical trials dedicated to preoperative systemic treatment in breast cancer. pCR became a surrogate of treatment effectiveness. That is why oncologists eagerly use polychemotherapy combined with dual HER2 blockade as preoperative treatment to increase the patient's chance to achieve pCR, sometimes even when the patient's risk of relapse is relatively small. The goal of this article is to review current evidence-based knowledge about the effectiveness and toxicity of polychemotherapy with or without anthracycline combined with trastuzumab or dual HER2 blockade used as preoperative treatment in HER2-positive breast cancer patients.

Key words: pertuzumab, anthracycline, preoperative chemotherapy, pathologically confirmed complete response (pCR), breast cancer, overall survival

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General principles of preoperative chemotherapy

The classic indication for systemic preoperative treatment in breast cancer patients is the local and/or regional advancement, e.g. T3-T4 N0-3 or T1-4 N2-N3 (LABC, locally advanced breast cancer). In patients with initially inoperable tumors, preoperative pharmacotherapy enables radical local treatment. On the other hand, in patients with cancer that is initially operable, but requires mastectomy, the goal of preoperative treatment is to enable breast-conserving surgery (BCS). In both cases, preoperative chemotherapy plays the role of induction treatment. In primary operable patients, preoperative chemotherapy is called neoadjuvant chemotherapy (NAC).

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In practice, however, the terms inductive and neoadjuvant are often used interchangeably.

The benefit of combined modality treatment with induction chemotherapy in patients with inoperable locally advanced breast cancer was demonstrated already several decades ago. The 1983 study by Pawlicki et al. [1] included 87 patients with inoperable LABC, 72 of whom were diagnosed with inflammatory cancer. The 3-year overall survival rate in patients who underwent surgery was over 60%, in patients undergoing radiotherapy it was 32% and only 12% in patients without local treatment.

A more recent 2017study by Wang et al. [2] also points to surgery preceded by induction chemotherapy as a method ensuring long-term survival in patients with initially nonoperative tumors. Literature data show that currently patients with locally advanced inoperable cancer qualified for preoperative chemotherapy account for 3.5% of all patients with newly diagnosed breast cancers. This percentage may differ between regions with different availability of screening tests, but precise data are lacking. According to the Surveillance, Epidemiology, and End Results (SEER) database [3], 29% of newly diagnosed US patients have regionally advanced diseases. According to data from Great Britain and Germany, the percentage of patients diagnosed with stage III is about 10–13% [4, 5]. However, it should be noticed the last data refer to primarily stage III operable and inoperable cancer.

Similarly, as adjuvant therapy, systemic preoperative treatment aims also to reduce the risk of recurrence and death. It has been shown that in patients with operable breast cancer, administration of chemotherapy before surgery, as compared to its administration after surgery, has a similar effect on life prolongation. This was confirmed, *inter alia*, in the meta-analysis published in 2018 [6], which included almost 5000 patients participating in 10 randomized clinical trials started before 2005. The median follow-up was 9 years. Patients were subjected to various NAC regimens: CMF, anthracycline-based regimens, and regimens containing anthracycline and taxane. The use of NAC resulted in a clinically assessed response in 69% of patients and allowed for a conserving surgery in a higher percentage of patients (65% *vs.* 49%). There were no significant differences between the efficacy of preoperative and adjuvant chemotherapy in terms of the risk of dissemination within 15 years (38.2% *vs.* 38.0%; RR 1.02; p = 0.66), death due to breast cancer (34, 4 *vs.* 33.7%; RR 1.06; p = 0.31), or all-cause death (40.9% *vs.* 41.2%, RR 1.04; p = 0.45). It should be emphasized that in the group of patients receiving preoperative chemotherapy, more local relapses were noted within 15 years (21.4% *vs.* 15.9%, RR 1.3; p = 0.0001), which indicates an extremely important role of precise tumor marking before initiation of NAC, meticulous histopathological evaluation, and adequate use of adjuvant radiotherapy.

The response to NAC assessed in the histological examination was classified into 4 categories — it can be a complete response confirmed microscopically (pathologic CR, pCR, residual cancer burden 0, and RCB 0) or residual disease of various extension: minimal RCB-I, moderate RCB-II, and extensive RCB-III. The extension of residual disease is calculated with the use of calculators taking into account the size of the primary and residual tumor (mm), "cellularity" of the residual tumor (%) number of lymph nodes involved, and size of the largest metastasis (mm). A complete response confirmed microscopically (absence of infiltrating cancer in the breast and removed regional lymph nodes) is associated with a significant improvement in prognosis compared to no such response, which was confirmed for all breast cancer subtypes [7]. Therefore, using chemotherapy before surgery provides prognostic information that is not available in the case of adjuvant treatment. In some patients with poorer prognoses, who did not achieve pCR, further adjuvant therapy (e.g. trastuzumab, emtansine, capecitabine) may be used [8, 9].

Preoperative chemotherapy used in clinical trials makes it possible to assess the effectiveness of new drugs, determine response biomarkers (predictors), learn about the biology of the disease, or use treatment escalation or de-escalation.

Clinical dilemmas related to the indications for NAC and the choice of treatment regimen in HER2+ patients

Due to the similar effectiveness of pre- and postoperative chemotherapy in terms of its impact on prognosis, with simultaneous additional benefits of preoperative systemic treatment (information on prognosis, response-dependent treatment individualization), the indications for preoperative chemotherapy have now significantly expanded. Murphy et al. [10] collected data from patients with invasive breast cancer treated with perioperative chemotherapy and surgery between 2010 and 2015. In this period, there was a significant increase in the percentage of patients receiving preoperative chemotherapy ($p < 0.001$) for all breast cancer subtypes. The highest percentage of patients receiving NAC and the largest increase in the percentage of such patients concerned individuals with the so-called triple-negative breast cancer (TNBC) and HER2+ breast cancer. It is noteworthy that among HER2 + patients, the increase in NAC use frequency particularly concerned patients with stage I and II tumors (HR+/ /HER2+: TNM I from 3.7% to 13.3%; TNM II from 22.6% to 49.4%; TNM III from 46.2% to 54.5%; HR–/ /HER2+: TNM I from 3% to 17.4%; TNM II from

25.2% to 52.4%; TNM III from 54.3% at 54.9%). A similar phenomenon occurred among patients with TNBC.

This new tendency is confirmed by the recommendations of scientific societies. According to the recommendations of the European Society of Clinical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), the use of preoperative systemic treatment in patients with TNBC and HER2+ cancer should be considered if the primary tumor diameter is > 2 cm, regardless of the involvement of regional lymph nodes [11, 12]. In patients with HER2+ breast cancer, preoperative chemotherapy should be combined with anti-HER2 targeted drug(s).

The value of trastuzumab (T) in perioperative treatment in terms of improved prognosis has been well documented, but mainly in adjuvant therapy studies. A meta-analysis by Moja et al. [13] showed that adjuvant treatment with trastuzumab initiated with taxane-containing chemotherapy reduces the relative relapse risk by 46% and death risk by 36%.

In Poland, perioperative treatment with anti-HER2 drugs is financed under the MoH drug program. According to the current regulations (as of March 2022), patients with a breast tumor larger than 1 cm or with the N+ feature are eligible for preoperative treatment with trastuzumab. On the other hand, the criterion for dual HER2 blockade use (trastuzumab with pertuzumab, TP) is tumor diameter > 2 cm with associated lymph node involvement or lack of hormone receptors expression. The drug program does not specify which chemotherapy regimen should be combined with trastuzumab or dual HER2 blockade. However, it indicates that the total duration of active pertuzumab therapy in preoperative treatment in combination with trastuzumab and chemotherapy ranges from 3 to 6 infusions. In practice, the treating physician may choose from 4 possible chemotherapy regimens: classic sequential treatment with an anthracycline and taxoid in combination with trastuzumab, or a dual HER2 blockade (most often 4 × AC → 12 × paclitaxel/4 × docetaxel + T or TP), or docetaxel with carboplatin in combination with trastuzumab (TCH), or dual HER2 blockade (TCHP). The great flexibility in qualifying for multi-drug preoperative chemotherapy in patients with relatively less advanced disease may lead to some confusion, especially if one keeps in mind the fact that in patients with pT1N0 tumors, only chemotherapy with paclitaxel and trastuzumab is considered adequate adjuvant treatment [14].

Moreover, the current NCCN recommendations indicate chemotherapy without anthracycline as the preferred chemotherapy in perioperative treatment. This choice is justified by its lower toxicity, especially to the heart.

The purpose of the further part of this article is to present the current evidence-based knowledge regarding benefits of anthracyclines abolition and using pertuzumab in preoperative treatment in HER2+ patients.

What is the benefit of adding pertuzumab to preoperative treatment?

A pivotal study for pertuzumab in preoperative treatment was NEOSPHERE [15], an uncovered phase-II study in which patients with HER2+ breast cancers were assigned to 4 arms with perioperative systemic treatment. As part of preoperative treatment, patients received 4 treatment cycles according to the following schedules: 1) trastuzumab + docetaxel, 2) pertuzumab + trastuzumab + docetaxel, 3) pertuzumab + trastuzumab, 4) pertuzumab + docetaxel. After surgery, all patients received 3 cycles of adjuvant FEC chemotherapy, except for patients in group 3 who received 4 cycles of docetaxel and then 3 cycles of FEC. The primary study endpoint was pCR assessed in the breast only. Patients receiving pertuzumab and trastuzumab with docetaxel had significantly more pCR in the breast (46%) compared to the group treated with trastuzumab and docetaxel (29%, p = 0.014). When interpreting the results of this study, it should be remembered that systemic treatment was unusually split into preoperative and postoperative phases, and pCR was assessed atypically (only in the breast, not in the breast and lymph nodes).

However, the greater effectiveness of dual HER2 blockade in combination with chemotherapy in terms of pCR rate compared to trastuzumab with chemotherapy was confirmed in meta-analyses. The Wu et al. study (2019) compared various preoperative treatment regimens in HER2+ patients, ranging from chemotherapy alone to chemotherapy with dual HER2 blockade, including pertuzumab and trastuzumab [16]. The authors showed that chemotherapy in combination with trastuzumab, compared with its combination with trastuzumab and pertuzumab, is associated with a significantly lower chance of obtaining pCR, but there is no significant difference in the percentage of patients undergoing conserving treatment. The authors also showed no significant differences in the toxicity of both treatment forms.

Unfortunately, the question of whether adding pertuzumab to preoperative chemotherapy combined with trastuzumab improves the prognosis remains unanswered. Although disease-free survival (DFS) was one of the secondary endpoints in the NEROSPHERE study, the trial was not statistically powered to formally test the hypothesis, and the results were only descriptive. The 5-year DFS rates were 81% in subgroup 1, 84% in

subgroup 2, 80% in subgroup 3 and 75% in subgroup 4, respectively [17].

Some insight into the effect of pertuzumab used in perioperative treatment on life extension may be provided by the APHINITY analysis — phase-III randomized, double-blind clinical study [18]. It aimed to evaluate the benefit of adding pertuzumab to standard postoperative chemotherapy in combination with trastuzumab. Almost 5000 patients with operable breast cancer, undergoing primary radical surgery were randomly assigned to 2 arms: standard adjuvant treatment with or without pertuzumab, which was administered together with trastuzumab for 1 year. In total 22% of patients received chemotherapy without anthracyclines, and 63% of patients had lymph nodes involved. The primary study endpoint was invasive disease-free survival (IDFS), secondary endpoints included, among others, OS, DFS, safety, and quality of life. Following the publication of the primary endpoint results, the study was considered formally positive. The 3-year estimated IDFS rates were 94 *vs.* 93%; hazard ratio (HR) = 0.81, 95% confidence interval (CI) 0.66–1.00, p = 0.045.

After 74 months of follow-up and a second OS interim analysis, a 3pp difference in IDFS was confirmed (6-year IDFS rates 91% *vs.* 88%; HR = 0.76; 95% CI 0.64–0.91) in favor of treatment with pertuzumab [19]. However, no significant OS difference was found. The subgroup analysis indicated that the benefit of pertuzumab was primarily noted in patients with infiltrated lymph nodes (IDFS 88% *vs.* 83%; HR = 0.72; 95% CI 0.59–0.87).

In conclusion, dual HER2 blockade compared to trastuzumab alone, added to chemotherapy, significantly increases the chances of obtaining pCR but does not significantly affect the percentage of patients undergoing conserving treatment. Its effect on life extension is unknown. Extrapolation of the APHINITY study results suggests that patients at high recurrence risk (lymph node(s) metastases) may slightly benefit in terms of IDFS extension from pertuzumab treatment, but this applies to one-year use, not short-term use, only during preoperative therapy.

Should anthracyclines be abandoned in preoperative treatment? Scientific evidence

The starting point for the discussion on resignation from anthracycline in adjuvant chemotherapy in patients with HER2+ breast cancer was the BCIRG006 study published in 2011 [20] and updated in 2015 [21]. Three thousand two hundred patients with HER2+ breast cancer, 70% of whom had lymph nodes infiltrated, were randomized to 3 arms. Within the standard treatment, patients received 4 cycles of AC sequentially, followed by 4 cycles of docetaxel 100 mg/m^2. In the first experimental arm, the above chemotherapy was combined with trastuzumab (immunotherapy was started together with 1 administration of docetaxel). In the second experimental arm, patients received 6 courses of the TCH regimen (trastuzumab, docetaxel 75 mg/m^2, and carboplatin AUC × 6). Trastuzumab was continued for up to 1 year in both treatment arms. It should be noted that in the TCH regimen, trastuzumab treatment started earlier after surgery compared to sequential treatment. The primary endpoint was disease-free survival, the secondary endpoints were overall survival, safety, and determination of molecular predictors [topoisomerase 2 alpha gene (*TOP2A*) amplification]. Both treatment regimens with trastuzumab turned out to be more effective than sequential chemotherapy in terms of DFS and OS, also in patients with lymph node involvement.

Unfortunately, the study was not designed to compare the regimens with trastuzumab. There was minimal numerical superiority of the anthracycline regimen. According to the 10-year DFS rate, the difference amounted to 1.6 percentage points, and for the OS — 2.6 percentage points. In lymph node-positive patients, the difference in the 10-year DFS rate was also minimal (sequence 69.6% *vs.* TCH 68.4%). The TCH regimen was favored by the toxicity profile of long-term cardiac and hematological complications. The anthracycline-free regimen induced significantly fewer left ventricular ejection fraction (LVEF) reduction to grade 3–4 (0.4% *vs.* 2%) and significantly fewer relative LVEF reduction of more than 10% (9% *vs.* 19%). Acute leukemia was diagnosed in 2 patients treated sequentially and 1 patient in the TCH group. Febrile neutropenia was equally common in both trastuzumab arms (approx. 10%), while anemia and thrombocytopenia were more common in patients treated with TCH. Subgroup analyses taking into account the amplification of the *TOP2A* gene, present in 35% of patients, indicated that in such patients sequential chemotherapy without trastuzumab was as effective as chemotherapy with trastuzumab in terms of DFS. This phenomenon was not observed in patients without *TOP2A* gene amplification.

It is hypothesized that the high efficacy of the TCH regimen (or other non-anthracycline regimens) used in perioperative therapy is due to the earlier initiation of anti-HER2 therapy. This may be indicated by the results of a retrospective study by Gallo et al. [22]. It is an analysis of data from 506 patients treated with trastuzumab in combination with perioperative chemotherapy (adjuvant 76%, neoadjuvant 24%) in a center in Dublin since 2010, collected in the "One Thousand HER2 Patients Project" database. About 70% of patients included in the analysis received treatment in which trastuzumab was initiated together with chemotherapy start

(TCH regimen or similar), about 17% were given sequential chemotherapy with trastuzumab administered concurrently with taxane, 6.7% received trastuzumab after chemotherapy completion, and 6.7% — trastuzumab without chemotherapy. It turned out that patients who started immunotherapy together with taxoid in sequential treatment or after completion of all chemotherapy were characterized by an increased relapse risk compared to patients receiving trastuzumab commenced simultaneously with the start of chemotherapy (TCH regimen or similar, DFS HR = 1.86; 95% CI 1.11–3.09; p = 0.017). The difference in OS was not statistically significant (OS HR = 1.18; 0.59–2.34; p = 0.629). However, when interpreting the results of this study, it should be remembered that it was a retrospective analysis, and the prognoses of patients qualified for sequential chemotherapy containing anthracycline and taxane could be worse at baseline.

An example of a phase-II randomized study evaluating the safety and effectiveness of systemic preoperative treatment with or without anthracyclines in HER2+ patients is TRYPHAENA [23]. The study included 225 patients with operable, locally and regionally advanced, or inflammatory breast cancer with a primary tumor diameter greater than 2 cm. In all three arms, patients received trastuzumab and pertuzumab in combination with 6 cycles of chemotherapy: arm 1: 3 × FEC + T + P → 3 × docetaxel + T + P; arm 2: 3 × FEC → 3 × docetaxel + T + P; and arm 3: 6 × docetaxel + carboplatin + T + P. After surgery, treatment with trastuzumab was continued for a total of 1 year. The primary endpoint of the study was safety and tolerability, with secondary endpoints including DFS and OS. There was no formal testing of the research hypothesis in the study, and the results were presented descriptively. The 3-year DFS rates were 87%, 88%, and 90%, respectively, and the OS rate was 94%, 94%, and 93%, respectively [24].

The assessment of the effectiveness of preoperative chemotherapy with or without anthracyclines in combination with dual HER2 blockade was also the aim of the randomized phase-III TRAIN-2 study, which enrolled 438 patients with stage II and III HER2+ breast cancers [25]. The two preoperative treatment arms were 3 × FEC + trastuzumab + pertuzumab → 6 × paclitaxel (80 mg/m^2, days 1 and 8) + carboplatin (AUC × 6) + trastuzumab + pertuzumab or 9 cycles of paclitaxel + carboplatin + trastuzumab + pertuzumab. All patients received trastuzumab for up to 1 year after surgery and underwent radiotherapy and adjuvant hormone therapy if indicated. The primary endpoint was pCR, secondary endpoints included event-free survival (EFS) and OS. After a median follow-up of 49 months, there were no significant differences neither in pCR, or 3-year event-free survival rates, or OS. Among patients treated without anthracycline there were significantly fewer cardiac adverse events (8.6% *vs.* 3.2%, p = 0.021) or febrile neutropenia. When analyzing the results of the study in terms of practical conclusions, it is worth noting that in both arms (as in the TRYPHAENA study) dual HER2 blockade was used, so results do not apply to patients treated only with trastuzumab combined with chemotherapy. Moreover, the chemotherapy used in both arms was non-typical, longer than the standard one (9 cycles), paclitaxel in sequential treatment was combined with carboplatin and not used as monotherapy, trastuzumab and pertuzumab were administered simultaneously with an anthracycline (which is not recommended outside of clinical trials).

In many countries, pertuzumab is not available in preoperative treatment for economic reasons. Therefore, the goal of the uncovered phase-II randomized neoCARH study was to evaluate using anthracyclines as part of preoperative chemotherapy in combination with trastuzumab only [26]. Standard adjuvant treatment was continued after surgery. The study was conducted in Chinese centers, and patients were assigned to 2 arms with the standard chemotherapy used in adjuvant treatment: sequential treatment 4 × EC → 4 × docetaxel + trastuzumab or 6 × TCH. The primary study endpoint was pCR, with secondary endpoints including DFS and OS. Only 135 patients were enrolled in the study. It was shown that the pCR rate was significantly higher in patients treated with the TCH regimen compared to the sequential therapy (56% *vs.* 37%, p = 0.032), but no significant difference was found in the percentage of patients who underwent conserving surgery (p = 0.139). Survival results are not yet mature.

However, the superiority of the TCH regimen over sequential treatment with trastuzumab in increasing the chance of pCR remains controversial if taking into account the results of the meta-analysis by Pelizzari et al. [27] presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting [27]. The meta-analysis included randomized phase II and III studies and compared the effectiveness of different preoperative treatment regimens in HER2+ patients in terms of pCR rate. An indirect comparison of the different treatment regimens was performed. PCR rates after various treatment regimens were estimated using Bayesian statistics. The authors found no statistically significant difference between the effectiveness of dual HER2 blockade combined with chemotherapy with anthracyclines as compared to its combination with chemotherapy without anthracyclines. Similarly, there was no significant difference between the combination of trastuzumab and anthracycline chemotherapy compared to its combination with chemotherapy without anthracyclines. However, a significant difference was found in favor of dual HER2 blockade in combination

with anthracycline chemotherapy compared to trastuzumab with anthracycline chemotherapy. Moreover, dual HER2 blockade combined with chemotherapy without anthracyclines turned out to be significantly more effective in inducing pCR compared to trastuzumab combined with anthracycline chemotherapy. The authors also estimated the chances of obtaining pCR depending on the treatment regimen, and they were as follows: dual HER2 blockade with chemotherapy containing anthracycline — 58%, dual HER2 blockade with chemotherapy without anthracycline — 54%, trastuzumab with chemotherapy containing anthracyclines — 44%, trastuzumab with chemotherapy without anthracycline anthracyclines — 36%.

In conclusion, there is a lack of reliable results from randomized clinical trials showing whether and how abandoning anthracyclines in preoperative chemotherapy combined with trastuzumab affects the prognosis. Extrapolation of the BCIRG006 adjuvant treatment study results suggests that the efficacy of the TCH regimen and sequential treatment may be comparable. When dual HER2 blockade is combined with preoperative chemotherapy, abandoning the anthracycline does not affect prognosis after a relatively short follow-up period, although the TRAIN-2 study used atypical chemotherapy regimens. The results of the meta-analysis of phase-III and II clinical trials indicate that the withdrawal of anthracyclines, either in the case of chemotherapy combined with trastuzumab or with dual HER2 blockade, does not significantly reduce the chance of pCR obtaining, although the numerically highest pCR rate should be expected after using dual HER2 blockade with chemotherapy containing anthracyclines. The same meta-analysis shows that dual HER2 blockade with anthracycline-free chemotherapy is significantly better in terms of pCR rate compared to the combination of trastuzumab with anthracycline-containing chemotherapy. On this basis, it is suggested that anthracyclines should be abandoned in favor of adding pertuzumab to preoperative treatment. Such modern treatment is considered less toxic, although it generates significantly higher costs. However, it should be remembered that there are no data on the impact of such treatment on the improvement of prognosis. There are also no studies currently comparing sequential chemotherapy with trastuzumab or TCH with TCHP regimens.

Resignation from anthracyclines to avoid cardiac toxicity

The choice of a preoperative chemotherapy regimen without anthracycline may be dictated by the desire to avoid potential cardiotoxicity in patients with additional risk factors for heart complications. The analysis of the BCIRG006 study results after 10 years of follow-up showed significantly fewer cardiac complications in patients treated with the TCH regimen compared to those treated with AC-TH. Congestive heart failure grade 3/4 occurred in 4 and 21 patients, respectively ($p = 0.0005$), and a relative reduction in LVEF of at least 10% was noted in 97 and 200 patients, respectively ($p < 0.0001$). Such differences in cardiotoxicity were not noted in the neoCARH study, but it was characterized by small sample size and a short follow-up period. Therefore, the TCH regimen is a reasonable choice for patients with an increased risk of cardiac complications.

There is a lack of reliable data from randomized clinical trials assessing perioperative treatment and if adding pertuzumab to the TCH regimen increases the risk of cardiological complications. Partial information on this subject is provided by the analysis of patients participating in the NEOSPHERE study receiving preoperatively 4 courses of docetaxel with trastuzumab (group 1) or 4 × docetaxel with trastuzumab and pertuzumab (group 2). No significant difference was detected between the mean values of the maximum LVEF decreases in these subgroups. LVEF reduction by 10–15% or absolutely less than 50% was reported in 1 (1%) and 3 (3%) patients, respectively, in groups 1 and 2 during neoadjuvant treatment, and in a total of 2 (2%) and 9 (8%) patients, respectively, during 5 years of follow-up. However, it should be remembered that after surgery, patients were given an anthracycline.

It was shown in the TRAIN-2 study that anthracycline withdrawal in the case of dual HER2 blockade significantly reduces the risk of cardiotoxicity (LVEF reduction of at least 10% or absolutely < 50% in 8.6% and 3.2%, respectively, $p = 0.021$), but the anthracycline was administered here simultaneously with trastuzumab and pertuzumab.

In conclusion, in patients with an increased risk of cardiac complications, the choice of the TCH regimen is safer. However, it is not known whether and to what extent adding pertuzumab to this regimen increases the risk of cardiac toxicity, which would prevent or interfere with the planned preoperative treatment and then the continuation of anti-HER2 treatment after surgery.

Escalation and de-escalation of preoperative treatment in HER2+ patients

When planning treatment, one should be guided primarily by the real benefit that the patient may derive, that is, first of all, choose medications that extend life. Subsequently, the possible treatment toxicity should be minimized. Unfortunately, making pCR the primary endpoint for almost all studies evaluating the effectiveness

of NAC and thus assuming that pCR is a prognostic surrogate, introduced some information chaos. pCR began to be taken as a value in itself, which is as inaccurate as shown above. Consequently it has not been possible to demonstrate that an increase in the pCR rate by a given NAC regimen contributes to life extension or the effect on life extension has not been reliably rated. Pusztai et al. [28] postulate several potential factors that may underlie the apparent paradox that increasing the pCR rate does not translate into extending the life of patients receiving more intensive treatment: 1 — the initial prognosis may be so good that the patient would be cured only after surgery or standard treatment would be sufficient, 2 — in patients with residual disease, the risk of relapse can be effectively reduced by adjuvant treatments, 3 — primary tumor and micrometastases may show different sensitivity to the drugs used, which would explain the appearance of distant metastases during subsequent observation in approximately 3–5% of patients with pCR.

Meanwhile, the use of preoperative multi-drug chemotherapy combined with dual HER2 blockade (therapy escalation) is dictated by the desire to increase the patient's chance of having pCR. The effect of the above strategy is that patients with a low risk of recurrence are subjected to too intensive treatment with an unknown benefit in survival. The escalation of preoperative treatment in HER2+ patients to obtain the highest pCR rate is understandable if the patient is able to receive adjuvant treatment with TDM1 as a practical consequence of not achieving a complete response. The effectiveness of such treatment was documented in the uncovered, randomized, phase-III KATHERINE study [8], which enrolled almost 1500 patients with HER2+ tumors and residual disease after preoperative treatment with trastuzumab administered for at least 9 weeks. Patients were assigned to 2 arms: 14 TDM1 administrations or 14 trastuzumab administrations. The exclusion criterion was the clinical T1aN0 and T1bN0 stage at the time of radical treatment initiation. Adjuvant hormone therapy and radiotherapy were conducted according to the local standard. In the case of discontinuation of TDM1 due to intolerance, it was possible to administer trastuzumab. The primary study endpoint was IDFS, with secondary endpoints including DFS, OS, and safety. Among the patients included, 72% showed the presence of hormone receptors, three-fourths received anthracycline-containing chemotherapy, and 18% also received pertuzumab in preoperative treatment, in 25% of patients the tumor was inoperable at the time of starting preoperative treatment. The first interim analysis performed after the median follow-up of 41 months showed significantly greater efficacy of the experimental treatment in terms of the 3-year IDFS rate, the absolute gain was 11 pp (88% *vs.* 77%; HR = 0.50; $p < 0.001$). However, OS extension has not been demonstrated so far (March 2022). Since March 2022, adjuvant treatment with TDM1 in patients with residual disease in the breast or axillary lymph nodes after preoperative taxane-containing chemotherapy combined with anti-HER2 therapy has been financed under the Ministry of Health Drug Program.

Attention should also be paid to the concept of de-escalation of preoperative treatment, explored in recent years [29, 30]. It assumes that some patients have a good prognosis and do not require multi-drug therapy with dual HER2 blockade and that less intensive treatment would be sufficiently effective with reduced toxicity. Unfortunately, we do not currently know the predictive factors that would enable the selection of the optimal de-escalated preoperative treatment, and such a procedure should not be part of routine clinical practice. Figure 1 shows a schematic comparison of systemic preoperative treatment regimens for HER2+ patients in terms of the effect on life extension, cardiotoxicity, and the chance for conserving treatment.

Conclusions

In patients with operable breast cancer, the impact of preoperative chemotherapy on the prognosis does not differ from the effect of the same chemotherapy given postoperatively.

Despite the criteria of the drug program enabling such management, the preoperative treatment of HER2+ patients with free lymph nodes and a tumor smaller than 2 cm seems unjustified. In such patients, there is a possibility of adjuvant treatment with paclitaxel and trastuzumab after the primary surgery, although such an approach is justified by the results of a study without a control group.

The use of dual HER2 double blockade with preoperative chemotherapy (compared to trastuzumab with chemotherapy) increases the chances of obtaining pCR but does not increase the chances of conserving treatment. The impact of adding pertuzumab to trastuzumab in combination with preoperative chemotherapy on the prognosis is unclear. Extrapolation of the results of the adjuvant treatment study (APHINITY) suggests that addition of pertuzumab may improve prognosis in patients with high risk of recurrence (metastases in axillary lymph nodes). However, there are no data to suggest that short administering of pertuzumab only in preoperative treatment is as effective as 1 year lasting postoperative treatment.

The claim that anthracycline can be abandoned in preoperative chemotherapy in combination with trastuzumab or dual HER2 blockade without adversely affecting prognosis is based on an extrapolation from the adjuvant treatment study BCIRG006 and the TRAIN-2 study (including a small group of patients,

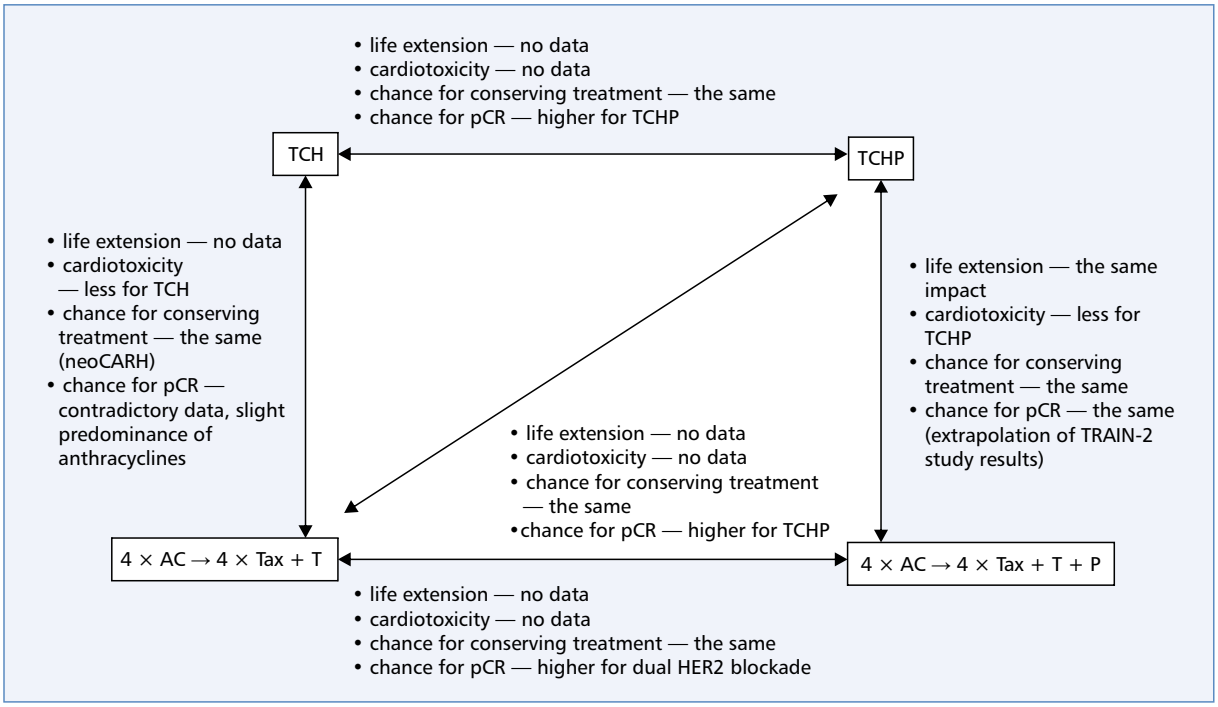

Figure 1. Schematic comparison of the preoperative treatment methods in HER2+ patients in terms of the effect on life extension, cardiotoxicity, and the chances of breast-conserving surgery (BCS) and pCR; TCH — docetaxel with carboplatin in combination with trastuzumab; TCHP — docetaxel with carboplatin in combination with dual HER2 blockade; AC — doxorubicin with cyclophosphamide; Tax — taxoid (docetaxel or paclitaxel); T — trastuzumab; P — pertuzumab; pCR — pathologically confirmed complete response

with atypical preoperative chemotherapy regimens and short follow-up).

There are no data from studies that directly compare preoperative chemotherapy with TCH and TCHP, or sequential treatments with trastuzumab and TCHP, in terms of their effect on survival and cardiac toxicity.

The TCH regimen is less cardiotoxic than sequential treatment with trastuzumab. There is no direct data on whether and to what extent adding pertuzumab to the TCH regimen increases cardiac toxicity.

In patients who do not achieve pCR after preoperative treatment, adjuvant therapy with TDM1 prolongs the invasive disease-free survival time, but the impact of such treatment on overall survival is unknown.

Conflict of interest

PP: fees for lectures, for conducting clinical trials, and covering the costs of participation in conferences from Roche Polska.

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CASE REPORT

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Stevens-Johnson syndrome in breast cancer patient treated with ribociclib

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ABSTRACT

Introduction. Ribociclib is a cyclin-dependent kinase (CDK) inhibitor, widely used in patients with different types of cancer. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic skin reactions that lead to epidermal necrolysis followed by exfoliation with life-threatening consequences.

Case presentation. We present a case of a patient with metastatic breast cancer with SJS-like skin reaction during treatment with ribociclib and letrozole. The patient presented skin changes, typical clinical symptoms (with Nikolsky sign), and destruction of the epithelium by forming blisters and abscesses on pathological examination. The lesions covered about 30% of the skin surface, and they were scored as grade 4 according to CTCAE v. 5.0. After ribociclib discontinuation and supportive management, a gradual improvement of skin lesions was observed.

Conclusion. We present this case as there are only a few case reports on ribociclib-related Stevens-Johnson syndrome in the literature, and clinicians should be aware of the risk of this side effect.

Key words: ribociclib, breast cancer, Stevens-Johnson syndrome, toxic epidermal necrolysis

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Established facts and novel insights

Established facts

- Ribociclib, an oral CDK inhibitor, is more increasingly used in daily clinical practice.
- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) could be life-threatening conditions.
- The sudden onset of bullous skin lesions should prompt immediate drug discontinuation, close monitoring, and dermatological evaluation.

Novel insights

- Cancer patients treated with ribociclib should be educated and closely monitored, even if they are in good general health state.
- Histopathological examination of samples taken during a biopsy of skin from the affected area is feasible and could diagnose SJS or TEN and introduce early treatment.

Introduction

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor, indicated in the treatment of patients with HR+/HER2– breast cancer in combination with aromatase inhibitor/fulvestrant, with proven significant improvement in progression-free/overall survival [1–3].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic skin reactions that may lead to epidermal necrolysis followed by exfoliation, with life-threatening consequences, such as loss of the skin barrier, dehydration, and possible multi-organ failure. They are differentiated based on body surface area affected (less than 10% is SJS, and more than 30% is TEN). Mortality is proportional to the extent of the skin damage and can exceed 40% in TEN patients [4].

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Although the rash is a common side effect associated with the use of ribociclib, bullous skin lesions of sudden onset were not reported in clinical trials.

We present a case of a patient with metastatic breast cancer with SJS-like skin reaction during treatment with ribociclib and letrozole.

Case report

A 67-year-old female patient was diagnosed with moderately differentiated, HER2-negative, stage IV (cT4cN1M1) breast cancer with lung, skin, and Th11 metastases.

Palliative spine irradiation and bisphosphonates were used in supportive treatment, and ribociclib and letrozole were commenced one month later. The medical history revealed compensated hypothyroidism, with chronic thyroid hormone supplementation and smoking (approx. 40 pack-years).

Two weeks after starting ribociclib treatment, skin dryness and an erythematous maculopapular rash appeared with a dark or purple tinge in the middle of the lesions located on the face, arms, and trunk. It was accompanied by a burning pain, sore and dry throat, and feeling dry eyes. After a few days, the rash turned into hemorrhagic blisters with accompanying epidermal shedding. There were erosions on the oral mucosa, making drinking and eating difficult. The treatment was continued, and the patient did not report to the doctor until the second treatment cycle was started. Then the intensity of lesions decreased for several days. The patient denied introducing new hygiene measures, changing detergents, or taking new medications or altenative medicines. The patient complained of painful skin sensations and itchiness. Pruritus grade 2, according to CTCAE v. 5.0, was diagnosed. Physical skin examination revealed small, partially confluent papules, erosions at the site of ruptured serous blisters, lesions with scabs in both mouth corners, and single erosions on the oral mucosa (Fig. 1A, B). Nikolsky sign, e.g. dislodgement of the intact superficial epidermis by a shearing force was also observed. The lesions covered about 30% of the skin surface, which was qualified as grade 4 according to CTCAE v. 5.0. The patient remained in a good general condition (PS = 1 according to ECOG).

Due to skin damage and the suspicion of SJS, ribociclib was discontinued, whereas letrozole was maintained. An elevated amount of neutral fluids, antihistamines, and close monitoring were recommended. According to the patient's report, the intensity of skin lesions on the visit day was slightly lower compared to the first days after their appearance. For this reason, calcineurin inhibitors were not introduced.

The comprehensive differential diagnosis was performed, including laboratory tests to exclude active and chronic HBV, HCV, and *Mycoplasma pneumoniae* infections. A history of Chlamydia pneumoniae infection

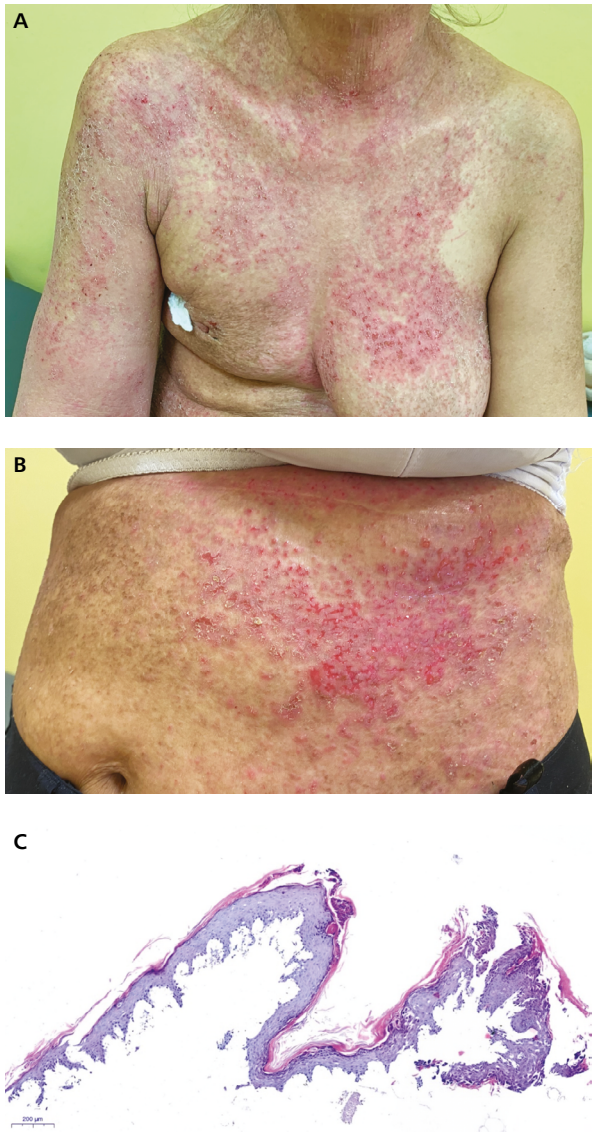

Figure 1. Skin lesion 2 weeks after symptoms onset (A, B) and pathological examination of skin biopsy (C)

was confirmed. The skin biopsies from the affected areas were performed (4 weeks after the first dermal symptoms). The histopathological examination revealed destruction of the epithelium with forming blisters and abscesses (Fig. 1C).

A gradual improvement of skin lesions was observed in the next few weeks, and it was decided to discontinue treatment with ribociclib and to continue monotherapy with letrozole.

Discussion

SJS and TEN are extremely rare (1–2 cases per million per year), life-threatening mucocutaneous reactions most commonly attributed to drug hypersensitivity.

They most frequently occur after administration of antibiotics, anticonvulsants, allopurinol, some non-steroidal anti-inflammatory drugs, and sertraline [5]. However, some infections (*Mycoplasma pneumoniae, Herpes simplex, hepatitis B and hepatitis C virus, Chlamydophila pneumoniae*) have been also reported as potential etiologies. Observational studies have shown an increased risk of SJS/TEN-related mortality and morbidity in patients with active cancer (relative risk, RR = 2.7), especially for hematological malignancies [6]. Therefore identifying SJS/TEN risk factors in this group of patients is particularly important. The previous publications highlighted the effect of immunosuppression, exposure to drugs triggering SJS/TEN (including antibiotics, immunomodulating drugs, cytotoxic agents), active neoplastic process, and their combination. The diagnosis is usually based on recent drug exposure that increases the risk of SJS or infection with *Mycoplasma pneumoniae*, as well as the presence of target-like skin lesions with central necrosis and mucosal involvement. Management of SJS and TEN consists in identifying the causative factors (discontinuing the suspected drug), inhibiting the reaction, if possible, and introducing intensive supportive care. As this is an extremely rare condition, the recommended algorithms are based on case series descriptions and therefore could be not definitive.

Currently, there are three CDK4/6 inhibitors approved for use in patients with advanced breast cancer. They are usually well-tolerated, and the most common side effect is neutropenia, which occurs in one to three quarters of patients (grade 3 or 4) but is usually asymptomatic and does not increase the risk of infection. Serious non-hematological adverse reactions are rare with a low treatment discontinuation rate. In clinical trials with CDK4/6 inhibitors, only rash and alopecia were reported among skin abnormalities. The prevalence of these skin lesions was similar for all discussed CDK4/6 inhibitors, with all-grade rash in < 20% of patients, and grades 3/4 in < 1% patients [2, 7].

A search of available medical literature databases found 4 case reports of SJS in patients treated with CDK4/6 inhibitors, including one case with simultaneous radiotherapy [8–11]. They described the varying degree of skin lesion severity, from only moderate to extensive, hemorrhagic mucous lesions, including rapid course and development of full-symptom life-threatening shock within several hours. Only in one case, the diagnosis of SJS was supported by a histopathological examination. The treatment included calcineurin inhibitor, glucocorticoids, and etanercept, an antibody against tumor necrosis factor α (TNF-α). One patient required hospitalization in a burn unit, and another one in an intensive care unit where drugs leading to hemodynamic stabilization and broad-spectrum empirical antibiotic therapy were administered. The authors of one report also highlighted the coexistence of psoriatic arthritis in a patient in remission.

A case of a female patient who underwent radiotherapy in the supraclavicular area while using palbociclib is of special interest [10]. She had a grade 3 (according to CTCAE, v.4.0) post-radiation esophageal and skin reactions, which resulted in hospitalization and intravenous hydration. In pivotal studies with CDK4/6 inhibitors, radiotherapy was continued to treat painful bone lesions, but anti-CDK4/6 treatment was stopped during radiotherapy. However, a synergistic effect of CDK4/6 inhibitor and radiotherapy is possible, enhancing G1-phase arrest of cell cycle and increasing cells' susceptibility to radiation during treatment with CDK4/6 inhibitors. Clinical trials with these combinations are ongoing [12].

In the presented case, radiotherapy was completed a month before ribociclib treatment. It involved a small area of skin on the back, so in our opinion, it had no effect on the SJS occurrence. The medical history and additional tests did not identify any other causes of SJS. We would like to highlight the feasible and useful skin biopsy. Although it did not reveal the typical lymphocyte infiltrations, the microscopic picture with features of epithelium destruction helped us to confirm the diagnosis and introduce specific treatment. CDK 4/6 inhibitors are well tolerated and become an established treatment option for patients with advanced breast cancer. However, it should not be forgotten that every drug can cause side effects, with serious and even life-threatening consequences. Pharmacovigilance is especially valuable in relation to recently introduced drugs to improve knowledge and reduce safety-related risks. Finally, the greater awareness of the risk of side effects, the more rational the management, which is of special importance in heavily treated cancer patients.

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Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Author contributions

AK — concept, draft manuscript preparation, decision about submission of the manuscript.

BR — concept, manuscript review, acceptance of final version, decision about submission of the manuscript.

Conflict of interest

Fees from: AstraZeneca, AMGEN, BMS, Gilead, Lilly, Merck, MSD, Novartis, Pfizer, Pierre-Fabre, Roche, Servier.

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VIA MEDICA

CASE REPORT

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Immunotherapy with pembrolizumab in a patient with advanced non-small-cell lung cancer with high PD-L1 expression and MET exon 14 splice site mutation

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ABSTRACT

Lung cancer is one of the major oncological problems in Poland. Pembrolizumab monotherapy can be applied as first-line treatment in patients with advanced non-small-cell lung cancer (NSCLC) with the expression of programmed death ligand 1 (PD-L1) in ≥ 50% of tumor cells. The article presents a case report of a female patient with advanced lung adenocarcinoma and high PD-L1 expression and an additional *MET* exon 14 skipping mutation. Despite the advanced stage of the disease, the patient benefited spectacularly from pembrolizumab administered following stereotactic radiotherapy for central nervous system (CNS) metastases. Partial remission followed by long-term stabilization of the disease was achieved. Unfortunately, the therapy was discontinued due to grade-3 pulmonary toxicity observed after 3 years of treatment. Despite the discontinuation of the pembrolizumab therapy, the disease has currently been stabilized and inflammatory changes have slowly resolved upon administration of corticosteroid.

Key words: non-small cell lung cancer, immunotherapy, splice site mutation, *MET* gene, PD-L1 expression

Oncol Clin Pract 2023; 19, 1: 63–68

Introduction

Pembrolizumab is a humanized monoclonal antibody directed against the programmed death 1 (PD-1) receptor on the surface of lymphocytes. Pembrolizumab monotherapy can be used as a first-line regimen in treatment-naive patients with advanced non-small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) expression in ≥ 50% of tumor cells [1].

The abnormalities of the *MET* gene are rarely detected in NSCLC patients. Assessment of *MET* gene disorders is recommended in patients with non-squamous NSCLC in the case of exclusion of mutations in the *EGFR* (*epidermal growth factor receptor*) gene and rearrangement of the *ALK* (*anaplastic lymphoma kinase*) and *ROS1* genes or simultaneously with the examination of these genetic abnormalities when the next generation sequencing (NGS) is used. The most common *MET* abnormalities include amplification of the gene and the exon 14 splice site mutation. The presence of this abnormality is an indication for the use of MET tyrosine kinase inhibitors, i.e. tepotinib or capmatinib [2].

We present a case report of a female patient with lung adenocarcinoma, who initially presented with persistent low-grade fever after a respiratory tract infection. The chemoradiotherapy resulted in short-term remis-

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sion of the disease. When the disease disseminated, the patient developed neurological symptoms related to central nervous system (CNS) metastases. Despite the advanced stage of the disease, the patient benefited spectacularly from the immunotherapy administered following stereotactic radiotherapy of the CNS metastases, although we detected a *MET* exon 14 skipping mutation. The benefits from the immunotherapy continue despite the discontinuation of the pembrolizumab treatment.

Case report

A 69-year-old woman who had not smoked for 25 years was admitted to the Department of Pneumonology, Oncology, and Allergology in summer 2017 due to a persistent low-grade fever after a recent respiratory infection. The chest X-ray (CXR) examination showed a round shadow in the left lung. Therefore, the additional diagnostics included chest and abdominal cavity computed tomography (CT), which revealed the presence of a peripherally located, smooth-bordered, left upper lobe lesion measuring 40 × 35 × 42 mm and enlarged left hilar, mediastinal, and subcarinal lymph nodes. Apart from the lung, there were no lesions suggesting distant metastases. The disease stage was initially classified as IIIB (cT2aN3M0). The patient's status was good (grade 1 according to the WHO/ECOG performance status scale). Due to the suspicion of a proliferative process, bronchoscopy with endobronchial ultrasound-guided thin needle aspiration (EBUS-TBNA) was performed. Pathological examination revealed pulmonary adenocarcinoma. Molecular tests did not show any abnormalities in the *EGFR*, *ALK*, or *ROS1* genes; however, a very high level of PD-L1 expression on the malignant cells was detected (90% of cells expressing the molecule).

The patient was qualified for sequential chemoradiotherapy, which started in September 2017. Imaging with CT performed after two cycles of combined cisplatin and vinorelbine chemotherapy showed partial response according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). The lesion in the upper lobe of the left lung was reduced to 24 × 25 mm. The mediastinal and hilar lymph nodes decreased to a maximum dimension of 14 mm in the long axis. Unfortunately, the positron emission tomography-computed tomography (PET-CT) examination performed after three chemotherapy cycles revealed the presence of a focal lesion with a moderate SUV (standardized uptake value) within the left suprarenal gland. The lesion had not been detected previously. Surgical consultation was conducted twice to qualify the patient for resection of the suprarenal gland. The patient was not qualified for surgery due to the probably benign nature of the lesion. After four chemotherapy cycles, the patient underwent radical radiotherapy at a dose of 62 Gy.

In May 2018, the patient presented with vertigo. Magnetic resonance imaging (MRI) of the brain revealed progression of the disease, inter alia three metastatic lesions in the central nervous system (CNS). The lesions were located in the right parietal region near the cerebellar falx, on the border of the pons and the right cerebellar peduncle, and in the right frontoparietal area (Fig. 1A–B). The patient was qualified for

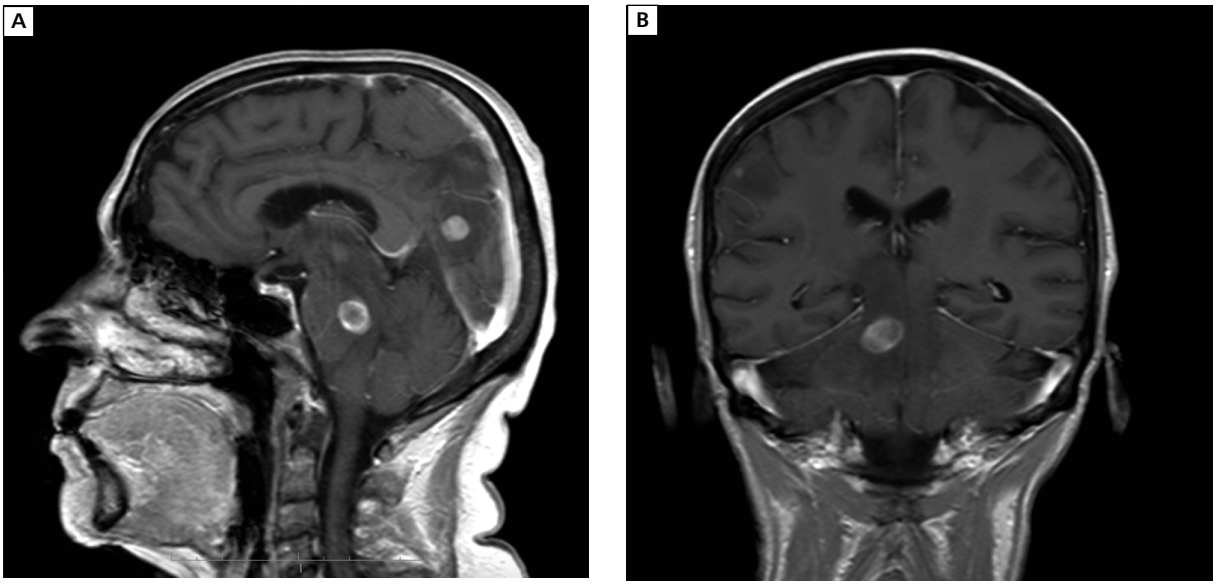

Figure 1. A. Magnetic resonance imaging of the brain in the sagittal projection showing metastatic lesions in the central nervous system located in the right parietal region near the cerebellar falx and on the border of the pons; **B.** Magnetic resonance imaging of the brain in the frontal projection showing metastatic lesions in the central nervous system located on the border of the pons and in the right frontoparietal area

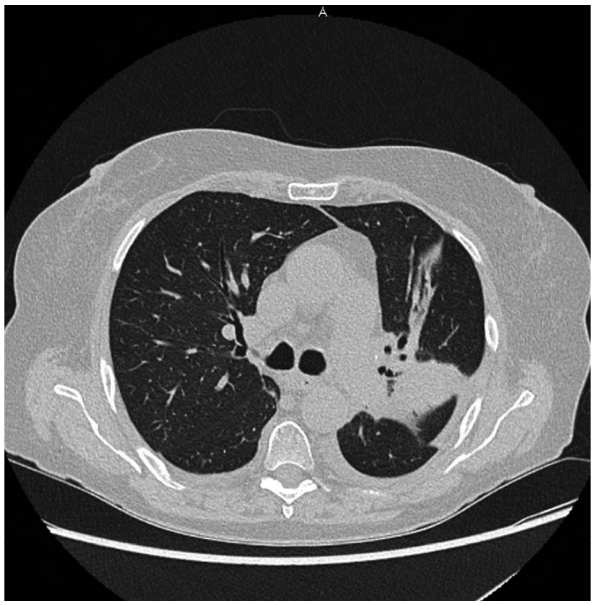

Figure 2. High-resolution chest computed tomography) showing the presence of lesions that could represent pseudoprogression, inflammatory lesions, or radiotherapy-induced perihilar infiltrative lesions on the left side

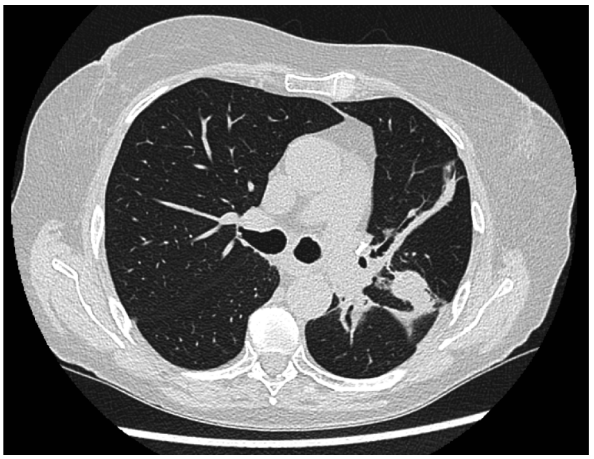

Figure 3. High-resolution chest computed tomography of the lung showing regression of the lesions and partial remission of the primary lesion

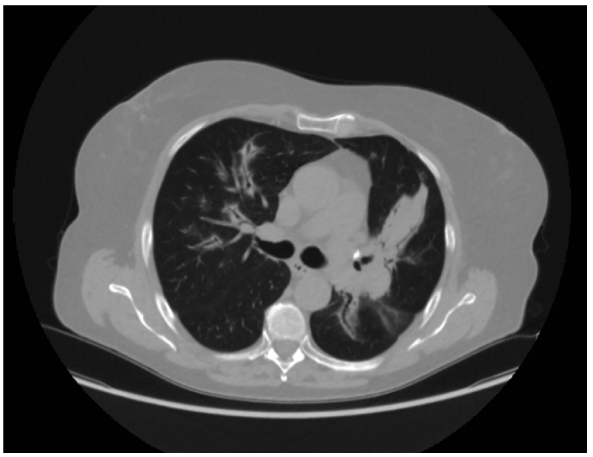

Figure 4. High-resolution chest computed tomography of the lung performed in February 2021, showing an untypical image of intense thickening of bronchial walls and peribronchial infiltrations in the lower lobes of both lungs and a 30 mm area of consolidation in the 5th segment of the right lung

stereotactic radiotherapy of the CNS metastases, which was performed in May 2018.

Given the radical aim of chemoradiotherapy applied in 2017, in June 2018 the patient was qualified for first-line pembrolizumab monotherapy at a dose of 200 mg every three weeks. Due to the good tolerance of the treatment, it was decided to increase the dose of pembrolizumab to 400 mg scheduled every six weeks in September 2019. Three days after the first administration of pembrolizumab in a higher dose, the patient was admitted to the hospital due to an episode of fever, general weakness, severe joint pain, and a moderate dry cough. The symptoms resolved quickly after appropriate treatment. Due to the above-described complications, a chest CT was performed. It showed the presence of lesions suggesting pseudoprogression, inflammatory lesions, or radiotherapy-induced perihilar infiltrative lesions on the left lung (Fig. 2). Pembrolizumab treatment was discontinued, and a control CT scan revealed regression of the new lesions and partial remission of the tumor and metastatic lymph nodes (Fig. 3). Immunotherapy was continued despite the high risk of intensification of the side effects. Gradual regression of malignant lesions was revealed. The patient reported feeling well throughout the treatment period. Imaging examinations of the CNS showed no recurrence or new metastases. A three-year progression-free survival (PFS) was achieved with the patient's well-being and high quality of life.

In February 2021, chest CT showed a very untypical image of intense thickening of bronchial walls and peribronchial thickenings in the lower lobes of both lungs and a 30 mm area of consolidation in the 5th segment of the right lung. The infiltrative lesion in the left lung cavity increased to 24 mm, and the area of the hilar consolidation increased to 45 × 22 mm (Fig. 4). Imaging of the chest showed four nodules in the apex of the right lung with a maximum size of up to 10 mm and two nodules in segment 6th of the left lung with a maximum size of 7 mm. The patient initially reported weakness, which she linked to the administration of the COVID-19 vaccine (Comirnaty). Subsequently, the patient reported dyspnea. The immunotherapy was discontinued in March 2021, after 33 months of treatment, due to suspected progression. Bronchoscopy was performed to confirm the nature of the infiltrative

and peribronchial lesions. No neoplastic cells were found in the collected material — pathology showed intense inflammatory lesions in the bronchial mucosa.

Given the clinical image, several additional genetic analyses were carried out. We conducted next-generation sequencing (NGS) examination using the Ion Torrent technology on the S5 sequencer (Thermo Fisher Scientific, Waltham, USA). We performed a simultaneous analysis of DNA and RNA isolated from tumor tissue from formalin-fixed paraffin-embedded (FFPE) block. DNA isolation was performed using the QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). RNA isolation was performed using the RecoverAll Total Nucleic Acid Isolation Kit for FFPE (Thermo Fisher Scientific, Waltham, USA). Sequencing was performed using the Oncomine Focus Assay (Thermo Fisher Scientific, Waltham, USA) allowing targeted sequencing and analysis of mutations, SNV (single nucleotide variation), and CNV (copy number variation) changes, as well as gene fusions in 52 genes related to the pathology of solid tumors. The NGS study showed the presence of a pathogenic skipping mutation in the *MET* gene, in the region of introns 13-15, which resulted in the deletion of exon 14 in the transcript. The mutation in the ClinVar or Varsome databases has a pathogenic status and is associated with the risk of osteofibrous dysplasia [3]. To confirm the NGS result, we conducted the RT-qPCR (reverse transcriptase-quantitative PCR) test using the Lung Cancer RNA Panel kit (EntroGen, Inc., Woodland Hills, Canada), which enables simultaneous assessment of the occurrence of *ALK*, *ROS1*, and *RET* gene fusions, as well as *MET* exon 14 skipping mutations in mRNA. The test result was positive for the *MET* skipping mutation and negative for the other targets.

The thorough analysis of the radiological image and histology, as well as a good response to corticosteroids, suggested that the lesions described above were unrelated to disease progression but were associated with another complication of the immunotherapy. Therefore, the patient did not receive pembrolizumab or any other systemic treatment and is now under close observation. Follow-up imaging studies revealed continuous regression of the inflammatory lesions in the lungs (Fig. 5). The persistent effectiveness of the pembrolizumab immunotherapy despite therapy discontinuation was demonstrated. Imaging of the brain performed in August 2021 showed no disease progression. Due to the concomitant *MET* gene abnormality, the patient may benefit from the treatment with MET inhibitors. However, given the stabilization of the disease, there are no indications for the administration of the next line of therapy. The patient is in a good general condition and her post-diagnosis survival time is now 4.5 years (January 2022).

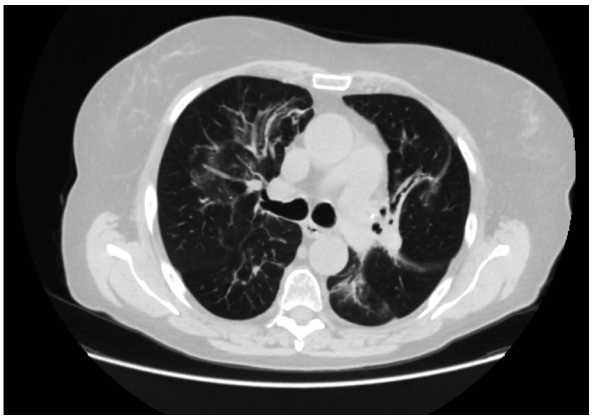

Figure 5. High-resolution chest computed tomography performed in December 2021 showing continuous regression of the inflammatory lesions in the lungs

Discussion

The case report presented here is unique for two reasons. The first reason is the 9-month persistence of the response to immunotherapy after discontinuation of the pembrolizumab treatment caused by grade 3 pulmonary toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 2.0. classification. Interestingly, pneumotoxicity appeared 3 years after the initiation of treatment. The second reason is the effectiveness of this immunotherapy in a patient with a rare mutation in the *MET* gene, that theoretically does not favor the effectiveness of immunotherapy.

The optimal duration of immunotherapy in cancer patients is unknown. Immunotherapy in clinical trials was used for up to 2 years or more in responding patients. However, it is observed that benefits from immunotherapy may persist after therapy discontinuation, regardless of the reason. Anti-PD-1 antibodies bind to the PD-1 receptor on circulating T lymphocytes for 3 months after a single dose of treatment [4]. Moreover, the effectiveness of immunotherapy is triggered by a persistent adaptive immune response through the activity of memory T cells that may be present for months [5]. In melanoma patients treated with pembrolizumab in clinical trials, a 2-year disease-free survival rate was reported in 67 of 105 complete responders who discontinued pembrolizumab and were observed without any anticancer therapy [6]. Similarly, long-lasting responses persisting despite treatment discontinuation have been reported in NSCLC patients treated with immunotherapy [7].

The CheckMate-153 clinical trial prospectively addressed the question about the optimal duration of immunotherapy [8]. Patients with pretreated advanced NSCLC with nivolumab efficacy after 1 year were randomized to two groups: the continuous nivolumab group *vs.* the observation group that resumed nivolumab

retreatment at disease progression. Patients treated with nivolumab continuously had a significantly longer PFS and insignificantly longer overall survival (OS) than the ones who discontinued immunotherapy [hazard ratio (HR) = 0.42 and HR = 0.63, respectively for PFS and OS]. These results suggested that treatment duration in patients who were benefiting from immunotherapy should last longer than 1 year [9].

Mesenchymal epithelial transition (*MET*) receptor alterations, including the *MET* exon 14 skipping mutation, are oncogenic in NSCLC and may induce patients' sensitivity to targeted therapy. The *MET* exon 14 skipping mutation is one of the rare molecular disorders observed in NSCLC patients. It usually occurs in elderly non-smoking females (over 75 years of age). It is considerably more frequent in patients with adenocarcinoma than in patients with squamous-cell carcinoma. The prevalence of splice site mutations in the *MET* gene is estimated at approximately 4–4.5% of NSCLC patients [10].

Tepotinib or capmatinib therapy should be the first-line treatment in NSCLC patients with *MET* exon 14 mutations. Certain efficacy of crizotinib, cabozantinib, and glesatinib in such patients has been also demonstrated [2]. Unfortunately, these drugs are not reimbursed in Poland and there is no routine testing for mutations in the *MET* gene. Therefore, NSCLC patients with this genetic abnormality most often receive first-line chemotherapy, chemoimmunotherapy, or immunotherapy, depending on the presence of comorbidities and PD-L1 expression on the tumor cells.

The presence of genetic driver abnormalities is usually associated with the low sensitivity of NSCLC patients to immunotherapy with anti-PD-1 or anti-PD-L1 antibodies. As shown by Gainor JF et al. [11], only 3.6% of NSCLC patients with *EGFR* gene mutations or *ALK* gene rearrangements responded to second-line immunotherapy, in contrast to 23.3% of patients without these genetic abnormalities. The median PFS in patients with *EGFR* gene mutations or *ALK* gene rearrangements receiving immunotherapy was only 2.1 months [11]. These observations were confirmed by clinical trials in which atezolizumab (e.g., OAK trial), nivolumab (CheckMate 057 trial), and pembrolizumab (KEYNOTE-010 trial) were used as second-line treatment. These studies involved 8–14% of NSCLC patients with *EGFR* gene mutations. The risk of death in the patients receiving the immunotherapy was higher or similar to patients receiving second-line chemotherapy (HR = 1.24, 1.18, and 0.88, respectively) [12–14]. As explained by the authors, single genetic driver abnormalities are associated with a low tumor mutation burden (TMB) and a low number of neoantigens. In turn, a small number of tumor-specific antigens results in low immunogenicity of the tumor, which is invisible to immune cells.

However, the situation in patients with splice site mutations in the *MET* gene is different. Spigel D et al. [15] assessed tumor burden mutation (TMB — mutations/Mb) using comprehensive genomic profiling (CGP). The top quartile of the number of somatic mutations in lung cancer patients was classified as high TMB. The mean number of somatic mutations in NSCLC patients with *MET* gene mutations was 6.2, which was almost twice as high as in patients with *EGFR* gene mutations and *ALK* gene rearrangements (4.5 and 3.1, respectively). About 10% of patients with *MET* mutations had a high value of TMB (more than 10 mutations/Mb) in comparison with 8% of patients with high TMB in the group with *EGFR* gene mutations and 4% of such patients in the group with *ALK* gene rearrangements. Moreover, almost half of NSCLC patients with splice site mutations in the *MET* gene had a moderate number of somatic mutations (elevated compared to an average TMB of 7.3) [15].

Sabari et al. [16] identified 111 patients with mutations in exon 14 of the *MET* gene. In this group, there were 41% of patients with high PD-L1 expression (≥ 50% of tumor cells with PD-L1 expression). The absence of PD-L1 expression was diagnosed in 37% of patients with *MET* gene alterations. The median TMB in patients with *MET* gene mutations was lower than that of unselected NSCLC patients in both independently evaluated cohorts: 3.8 *vs.* 5.7 mutations/Mb (n = 78 *vs.* n = 1769, cohort A) and 7.3 *vs.* 11.8 mutations/Mb (n = 62 *vs.* n = 1100, cohort B) [16]. In a study conducted by Maziers J et al., PD-L1 expression was found in 90% of patients with mutations or amplification of the *MET* gene [17].

The presented data showed that patients with *MET* exon 14 mutations usually exhibit high PD-L1 expression and quite high TMB. Therefore, the use of immunotherapy in these patients is justified in the second-line setting following the inability to use MET inhibitors. Patients with various genetic driver abnormalities were involved in the IMMUNOTARGET study, including 36 patients with mutations in exon 14 of the *MET* gene or with amplification of this gene. Most of the patients received second- or third-line immunotherapy. Disease control through immunotherapy was achieved in 50% of patients with *MET* splice site mutations, and partial response was observed in 15% of the patients. For comparison, disease control was achieved in 32–33% of patients with *EGFR* gene mutations and *ALK* gene rearrangements, and response to the treatment was observed in only 12% of patients with *EGFR* mutations and none of the patients with *ALK* gene rearrangements. The median PFS was 3.4 months, which was the longest time compared to that in patients with other genetic driver alterations (*EGFR*, *BRAF*, and *KRAS* gene mutations, *ALK*, *ROS1*, and *RET* gene rearrangements, and *HER2* gene ampli-

fication). Furthermore, the achievement of therapeutic response and long PFS depended mainly on the PD-L1 expression on tumor cells, which was frequently detected in patients with *MET* gene mutations. The median OS in patients with splice site mutations in the *MET* gene was 18.4 months, which is comparable to the median OS in patients without genetic abnormalities [17]. In a study conducted by Sabari et al. [16], the objective response rate to immunotherapy was 17% in NSCLC patients with *MET* exon 14 mutations, and their median PFS was 1.9 months (the number of response-evaluable patients was 24). The responses were not enriched in tumors with PD-L1 expression on ≥ 50% of tumor cells or with high TMB [16].

The present observations and findings reported by other authors confirm that pembrolizumab may be highly effective in NSCLC patients with the *MET* exon 14 skipping mutation, especially in the case of high PD-L1 expression on tumor cells [16–18]. These observations justify undertaking clinical trials based on the use of a combination of immunotherapy and therapy with MET tyrosine kinase inhibitors. A clinical trial (NCT03647488), which compared the efficacy of a second-line spartalizumab and capmatinib combination treatment *vs.* docetaxel, was conducted in NSCLC patients without a *MET* gene status assessment. The trial was unsuccessful as 55% of the patients had early disease progression and 28% had serious side effects of the therapy. However, only patients with advanced NSCLC with *MET* exon 14 skipping mutations are eligible for the ongoing trial NCT04323437. Although the results of this trial are still incomplete, the data reported in the present study encourage optimism.

Conflict of interest

Authors declare no conflict of interest.

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