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ORIGINAL ARTICLES

REVIEW ARTICLES

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) Sixth Edition.

1. The aim of the contest is to encourage submission of quality case reports related to oncological practice and to promote them in the scientific deliberations.
2. All respective manuscripts submitted to OCP between June 1st, 2021 and May 31st, 2022 and accepted for publication will qualify.
3. Manuscripts should be prepared in line with Authors' guidelines and should be submitted only through the manuscript system available at Journal's website: https://journals.viamedica.pl/oncology_in_clinical_practice
4. All submitted manuscripts will be evaluated during the peer review process and authors will be informed about their qualification for publication in OCP. Accepted papers will be evaluated by the Contest Committee based upon fulfillment of the Contest criteria as well as practical significance, originality, applicability and addressing of current/critical concerns.
5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
6. Results will be announced during the XXV National Congress of The Polish Society of Clinical Oncology and subsequently at the Journal website.
7. Winner will be notified via email.
8. Contest Committee may exclude a paper from participation in case of potential conflict of interest or ask submitting author for adequate clarifications.
9. The Sponsor at any stage and in any respect, will not participate in the evaluation of entries and selection of a winning paper.
10. The award amount shall be paid based on the copyright transfer agreement to the paper.
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ORIGINAL ARTICLE

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Results of darbepoetin alfa treatment of anaemia in chemotherapy-receiving breast cancer patients: a single-centre retrospective observational study

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ABSTRACT

A retrospective observational study of the outcomes of darbepoetin alfa treatment for chemotherapy-induced anaemia in breast cancer patients was conducted. A group of 152 patients treated during 13 months in one oncology centre was assessed. Ninety-eight patients (64.5%) received perioperative chemotherapy, and 54 patients (35.5%) received palliative chemotherapy. The results of treatment with darbepoetin alfa were analysed by age (< 65 *vs.* ≥ 65 years), the aim of chemotherapy (perioperative *vs.* palliative), and body mass index (< 25 *vs.* 25–29 *vs.* 30 and more). The effectiveness of the therapy was estimated at 80.9% (95% CI: 74.7–87.2%). Significantly higher effectiveness of ESA was found in patients treated perioperatively compared to patients treated for metastatic breast cancer (85.7% *vs.* 72.2%, p = 0.043). There were no differences in the effectiveness of ESA depending on age and BMI. No serious ESA-related adverse events were observed.

Key words: chemotherapy-induced anaemia, breast cancer, darbepoetin alfa, erythropoietin-stimulating agents

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Introduction

Erythropoietin-stimulating agents (ESA) are recombinant human erythropoietin preparations which stimulate bone marrow to produce red blood cells [1]. Apart from relieving anaemia symptoms, the application of ESA can prevent the necessity of the red blood cells transfusion in patients with chemotherapy-induced anaemia (CIA) [2] and thus avoid transfusion-related complications [3, 4]. During the COVID-19 pandemic no need for hospitalization in order transfusion of blood products is an additional value.

CIA is estimated to affect as many as 67% of patients undergoing chemotherapy [5]. Apart from the adverse influence on the patients' quality of life [6], CIA contributes to shortening the survival time of patients with solid tumours, lymphomas and myelomas [7].

Aim of study

The aim of the study is to assess the results of the application of darbepoetin alfa in the treatment of anaemia in patients undergoing chemotherapy for breast cancer.

Material and methods

A retrospective assessment was carried out of the results of darbepoetin alfa (Aranesp® manufactured by Amgen) treatment of 152 patients receiving chemotherapy for breast cancer in the Clinic of Breast Tumours and Reconstructive Surgery, National Institute of Oncology, Public Research Institute in Warsaw, in whom therapy was initiated in the period from 2 January 2019 to 16 February 2020. Darbepoetin alfa

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was administered to patients with both early and metastatic breast cancer. The drug was given to symptomatic anaemia patients, with a haemoglobin (Hb) level of 8–11 g/dL. In addition, it was also applied in chemotherapy-undergoing patients, with asymptomatic anaemia, with a haemoglobin concentration of < 8 g/dL. The indications were consistent with the position of Polish experts [8] as well as with the position of the ESMO [9].

In all the patients, Aranesp® therapy was initiated after prior and/or simultaneously with possible iron deficiency, B12 and folic acid supplementation as well as after exclusion of other, chemotherapy aside, causes of the occurrence of anaemia. All the patients received Aranesp® in the dose of 500 ug subcutaneously every 3 weeks. No other erythropoietin preparations were administered to the study group.

The results of darbepoetin alfa treatment were assessed retrospectively on the basis of changes in haemoglobin levels as well as the duration of the ESA therapy. The aim of the therapy was considered to have been reached when the Hb level increased by at least 1 g/dL within 4–6 weeks and when no indication for red blood cells (RBC) transfusion was seen in the course of ESA administration. The treatment was continued until a stable Hb level was reached, ensuring the security of further oncological treatment without the necessity of RBC transfusion or termination of chemotherapy.

The results of darbepoetin alfa treatment were analysed with reference to age (< 65 yrs. *vs.* ≥ 65 yrs.), aim of the chemotherapy applied (perioperative *vs.* palliative) as well as the body mass index (BMI), (< 25 *vs.* 25–29 *vs.* 30 and more).

What was also assessed, on the basis of patient documentation, were the side effects which could result from the application of ESA, with particular attention to thromboembolic complications, occurrence of pure red cell aplasia (PRCA) as well as anaphylaxis and allergic reactions of 3rd and 4th degree according to Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v.4.03) [10]. What was resigned from due to incomplete source documentation, was the assessment of the occurrence or exacerbation of venous hypertension as well as allergic reactions and injection site reactions. It should be emphasized that no patient was administered darbepoetin alfa after reaching an Hb level of ≥ 12 due to the possibility of a significant increase in the number of thromboembolic complications, in compliance with ESA application guidelines [8, 11].

Results

Group characteristics

The results of darbepoetin alfa treatment were assessed in a group of 152 subsequent patients, in the course of chemotherapy for breast cancer, in whom the administration of the preparation was initiated in the period from 2 January 2019 to 16 February 2020.

At the moment of the initiation of ESA administration, 33 patients (21.7%) were aged 65 or more (the oldest patient was 78 yrs.) while 119 (78.3%) were below 65 yrs. of age (the youngest patient was 28 yrs.)

Prior to the commencement of ESA treatment, 33 patients (21.7%) received intravenous iron supplementation. Ten patients (6.6%) in the course of ESA administration began intravenous iron supplementation simultaneously and 6 continued the intravenous iron supplementation started earlier. In total, 44 patients (28.9%) received iron preparations intravenously. Iron isomaltoside III in a dose of 1000 mg IV was administered in one or two doses during the observation period. No indication for vitamin B12 supplementation was found in any of the patients. It was not possible to determine exactly how many patients received folic acid-containing preparations. Oral iron preparations available on prescription were taken in the course of ESA therapy by 111 patients (73%). They included mainly *Ferri proteinatosuccinas* and iron sulphate II.

Red blood cells transfusion due to symptomatic anaemia and lack of response to ESA was necessary only in 17 patients (11.2%)

In the course of ESA treatment, perioperative chemotherapy was received by 98 patients (64.5%) and palliative chemotherapy by 54 patients (35.5%).

In the majority of patients (n = 108 patients, 71%), ESA treatment was initiated when a patient's Hb level was ≥ 10 g/dL while in 44 patients (28.9%), due to peripheral anaemia, when Hb level was above 10 but below 11 g/dL.

In the majority (90) of patients receiving perioperative chemotherapy the number of Aranesp® doses administered did not exceed 3, but 8 patients (5.3%) received 4 doses of the drug. Simultaneously, in the group receiving palliative treatment, as many as 20 patients received 4 or more doses of ESA, with 11 patients given 7 or more doses. It should be added that patients receiving more than 4 doses of ESA had them administered at time intervals longer than 3 weeks.

The group characteristics of the perioperatively treated patients, divided into two age groups, are described in Table 1 while that of the group of palliatively treated patients, also in two age groups, in Table 2. For the purpose of clarity, the patients were divided into four groups: 1 — early breast cancer (EBC) patients < 65 yrs. of age, 2 — early breast cancer (EBC) patients ≥ 65 yrs. of age, 3 — metastatic breast cancer (MBC) patients < 65 yrs. of age, 4 — metastatic breast cancer (MBC) patients ≥ 65 yrs. of age.

The Hb levels at the time of the first and the last ESA dose in individual groups are presented in Figure 1.

Table 1. Characteristics of early breast cancer (EBC) patients according to age group (Groups 1 and 2)

	Group 1 (EBC) < 65 yrs.	Group 2 (EBC) ≥ 65 yrs.	Total 1+2 (EBC)
Number of patients	80	18	98
Age: median (scope)	56 years (28–64)	69 years (65–76)	58 years (28–76)
Chemotherapy regimen:			
AC/PCL	28	6	34
AC/PCL+ carboplatin	9	0	9
TCH	25	7	32
TCH-P	6	2	8
Others	12	3	15
Hb level on the first dose of Aranesp®			
< 8 g/dL	1	0	1
8–10 g/dL	52	14	66
> 10 and ≤ 11 g/dL	27	4	31
Hb level on the final (or last during the observation period) Aranesp® dose			
< 8 g/dL	0	0	0
8–10 g/dL	9	2	11
> 10 g/dL	71	16	87
BMI 16–18.49 (underweight)	0	0	0
BMI 18.5–24.99 (normal value)	44	7	51
BMI 25–29.99 (overweight)	23	6	29
BMI 30–43 (obesity)	13	5	18
IV iron supplementation before and/or in the course of ESA application	25	4	29
Number of patients by the number of Aranesp® injections in the observation period			
1–3	72	18	90
4	8	0	8
5 and more	0	0	0

AC — doxorubicin with z cyclophosphamide; PCL — paclitaxel; TCH — docetaxel, carboplatin, trastuzumab; TCH-P — docetaxel, carboplatin, trastuzumab and pertuzumab; Hb — haemoglobin level; BMI — body mass index.

Effectiveness of darbepoetin alfa treatment

The estimated effectiveness of darbepoetin alfa therapy in the treatment of anaemia in patients receiving chemotherapy for breast cancer amounted to 80.9% (95% Cl: 74.7–87.2%).

Both the univariate and the multivariate analysis revealed statistically higher significant effectiveness in early breast cancer patients as compared with patients treated for metastatic breast cancer (85.7% *vs.* 72.2%, p = 0.043). The estimated odds ratio, OR = 2.330 (95% Cl: 1.015–5.351, p = 0.046).

No statistically significant differences in the ESA effectiveness were found depending on age or BMI. The estimated effectiveness in the < 65 *vs.* ≥ 65 years of age groups was 84.8% *vs.* 79.8%, respectively.

The estimated effectiveness values in the following BMI-dependent groups, namely: underweight + normal weight (the 2 groups were combined because there were only two patients with underweight: BMI: 16–24.99), overweight (BMI 25–29.99) and obesity (BMI 30–43.1), were 86.3%, 76.6% and 72.0%, respectively.

Side effects of darbepoetin alfa

Two patients (1.3%) with metastatic breast cancer were diagnosed with vascular access port thrombosis in the course of ESA therapy. In the remaining 150 patients, no other thromboembolic disturbances were observed. Nevertheless, it should be pointed out that 9 patients (9.2%) from the early breast cancer group and 12 (22.2%) from the group treated for metastatic breast cancer were treated with low molecular weight heparin as an adjuvant treatment (overall, 13.8%).

No case of pure red cell aplasia (PRCA) was reported. No case of anaphylaxis or significantly exacerbated (3rd or 4th degree acc. to CTCAE v. 4.03) allergic reaction were reported.

Table 2. Characteristics of palliatively treated patients (MBC, *metastatic breast cancer*) according to age group (Groups C and D).

	Group 3 (MBC) < 65 years	Group 4 (MBC) 65 years	Total 3 + 4 (MBC)
Number of patients	39	15	54
Age: median (range)	58 years (35–64)	71 years (65–78)	61 years (35–78)
Chemotherapy regimen:			
NPLD + CTX	7	0	7
Paclitaxel q7	8	5	13
Doxorubicin q7	7	5	12
Carboplatin + gemcytabin	3	0	3
Capecytabin	2	2	4
Others	12	3	15
Hb level on the first Aranesp® dose:			
< 8 g/dL	5	1	6
8–10 g/dL	22	13	35
> 10 and ≤ 11 g/dL	12	1	13
Hb level on the final (or last during the observation period) Aranesp® dose	2	2	4
< 8 g/dL	15	2	17
8–10 g/dL	22	11	33
> 10 g/dL			
IV iron supplementation before and/or in the course of ESA application	11	4	15
BMI 16–18.49 (underweight)	2	0	2
BMI 18.5–24.99 (normal value)	17	10	27
BMI 25–29.99 (overweight)	16	4	20
BMI 30– 43 (obesity)	4	1	5
Number of patients by the number of Aranesp® injections in the observation period	26	8	34
1–3	8	1	9
4–6	5	6	11
7 and more			

NPLD — non-pegylated liposomal doxorubicin; CTX — cyclophosphamide; q7 — every 7 days; Hb — haemoglobin level; BMI — body mass index.

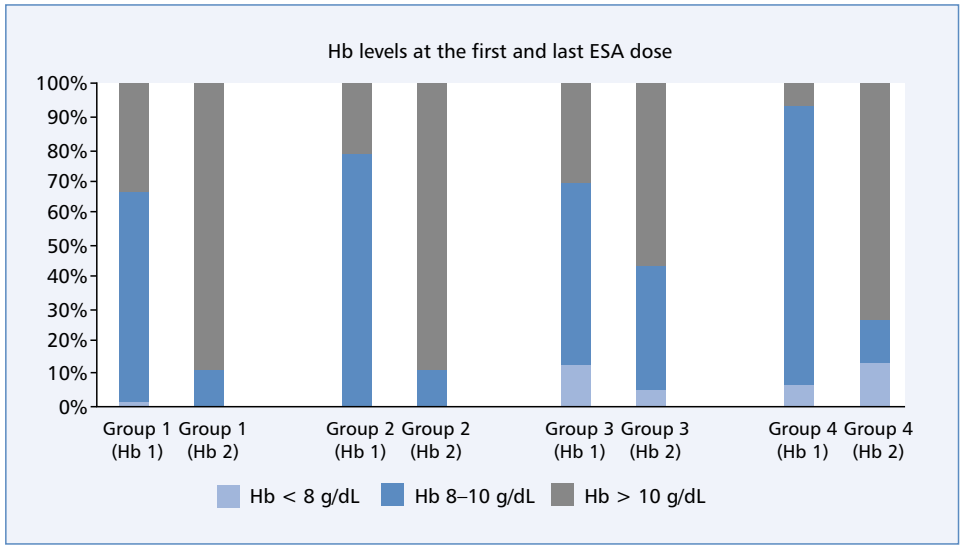

Figure 1. Hb level on the first (Hb 1) and last (Hb 2) Aranesp® dose in individual groups: 1 — perioperatively treated (EBC) patients < 65 years of age, 2 — perioperatively treated (EBC) patients ≥ 65 years of age, 3 — palliatively treated (MBC) patients < 65 years of age, 4 — palliatively treated (MBC) patients ≥ 65 years of age

Discussion

Chemotherapy-related anaemia constitutes one of the most common side effects in oncological patients [12, 13]. According to various authors, the incidence of anaemia in breast cancer patients is estimated at 6–97% [13, 14]. It has been most frequently reported in patients receiving docetaxel and carboplatin-based regimens [14, 15].

Red blood cells transfusions, iron preparations supplementation and erythropoiesis-stimulating drugs are recommended in CIA treatment depending on the severity of anaemia and the clinical situation [8, 9].

European guidelines suggest that ESA-group drugs should be applied primarily in patients with symptomatic anaemia who receive chemotherapy or a combination of chemotherapy and radiotherapy, with a haemoglobin concentration of 8–10 g/dL as well as in patients with asymptomatic anaemia who receive chemotherapy, with a haemoglobin concentration of < 8 g/dL. ESA administration can also be considered in patients with the Hb level of 10–11 g/dL, in the case of persisting symptomatic anaemia, after iron deficiency, B12 and folic acid supplementation and exclusion of other causes of anaemia [8]. Some authors advocate modification of ESMO guidelines and argue for more categorical recommendation of ESA, also in the last group of patients [16]. What is definitely not recommended is the application of ESA when the level of haemoglobin exceeds 12 g/dL [8, 9, 16].

In this study, the majority of patients (71%) had the ESA therapy initiated at the Hb level of ≥ 10 g/dL. Neither was Aranesp® administered in patients with an Hb level of above 12 g/dL.

Similar Hb values at the time of the initiation of ESA administration have been described in other observational studies. In the European observational CHOICE study, carried out in 11 European countries with the participation of 1900 patients with solid tumours, 57% of the included patients had an baseline Hb level of < 10 g/dL and 91% had < 11 g/dL [17].

The response rate to darbepoetin alfa in the study group was estimated at 80.9% (95% CI: 74.7–87.2%). This is consistent with the findings by other authors. In the clinical studies assessing the effectiveness of ESA in the treatment of CIA in different types of neoplasms, response rates ranged from 50 to 90% [18–22].

It is definitely worth emphasizing that our analysis confirmed statistically higher effectiveness of darbepoetin alfa in radically treated patients in comparison with patients treated in a palliative way (85.7% *vs.* 72.2%, p = 0.043). This is likely to be due to the complex aetiology of anaemia in patients with a generalized neoplastic disease and consequently worse response to ESA.

The perioperatively treated (EBC) patients received a significantly lower number of Aranesp® injections than the palliation-oriented chemotherapy (MBC) patients. This is consistent with expectations, as the duration of perioperative chemotherapy is strictly defined and ESA administration is not recommended in patients who have completed chemotherapy.

Numerous publications emphasize the necessity of a concurrent iron supplementation which improves ESA effectiveness [8, 9, 16, 19, 23].

In the group of patients covered by this study, almost one third (28.9%) received intravenous iron supplementation, which might have affected the obtained results of response to ESA. In addition, as many as 73% of the patients took oral iron supplementation which should, in turn, have no influence on the effectiveness of darbepoetin alfa [8].

The incidence of anaemia increases with age and some studies point to a significant growth in the incidence of anaemia in patients over 70 years of age [22]. Anaemia in the elderly leads to an increased number of falls as well as depression [23]. Although CIA is a common complication observed during chemotherapy of elderly patients, there is no information on a systematic clinical response to ESA in the elderly [23]. That is why this study strived to assess the effectiveness of the treatment with darbepoetin alfa in two age groups: below 65 years of age and 65 and more years of age. No statistically significant age-related differences were found in the effectiveness of ESA administration. Similar conclusions have been presented by other authors [13, 23].

In spite of the lack of relevant data in the literature, an attempt was made to assess the effectiveness of darbepoetin alfa depending on the BMI with the purpose of excluding the adverse influence of overweight and obesity on response to ESA. No statistically significant BMI-dependent differences in the effectiveness of Aranesp® were observed.

Numerous studies dealing with anaemia treatment discuss the question of the safety of ESA and RBC transfusion application [13, 24]. Both of these forms of treating anaemia involve the risk of thromboembolic complications. In addition, RBC transfusions have been reported to generate numerous immunological and non-immunological complications [25–27]. In this analysis, RBC transfusions concerned only 11.2% of patients in whom darbepoetin alfa treatment proved ineffective. This finding is worth emphasizing, particularly at the time of the COVID-19 pandemic when unnecessary hospitalization of chemotherapy-undergoing patients should be avoided.

Side effects of darbepoetin alfa in the study group were very rare. In 1.3% of the patients, thrombosis related to the earlier implanted venous access port was observed. No other thromboembolic complications were observed, which is inconsistent with relevant findings from the literature which describe these complications in about 20–30% of ESA-treated patients in the course

of chemotherapy for breast cancer [24, 28–30]. This very low percentage of thromboembolic complications can at least partly be attributed to the fact that 13.8% of the patients received concurrent adjuvant treatment with low molecular heparin.

This study is an observational study, performed retrospectively, and is thus of limited scientific value, but the presented findings are unique due to the collection of ESA-treatment data for a relatively large group of patients treated for breast cancer in one centre during nearly 13 months.

Conclusions

Darbepoetin alfa proved effective in the treatment of anaemia in chemotherapy-treated patients with breast cancer. The response to the treatment in the assessed group of patients was 80.9% (95% CI: 74.7–87.2%). Better response to darbepoetin alfa was found in early breast cancer (EBC) patients than in patients treated for metastatic breast cancer (MBC) (85.7% *vs.* 72.2%, p = 0.043). There were no statistically significant age- and BMI-related differences in ESA effectiveness. No significant side effects of darbepoetin alfa therapy were observed in either the EBC or the MBC group of patients.

Conflict of interest

The authors report no conflicts of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Which chemotherapy regimen might be the best for the second-line treatment of patients with small-cell lung cancer?

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ABSTRACT

Introduction. Small-cell lung cancer (SCLC) is an aggressive disease. Despite the first-line (1L) chemotherapy, almost all patients need the second-line (2L) treatment within a year. However, there is no general agreement on standard 2L treatment.

This study aimed to determine outcomes obtained with different treatment regimens, factors affecting the results, and standard approach in the 2L treatment of SCLC.

Material and methods. This was a singlecenter, retrospective, cross-sectional, cohort study. The inclusion criteria were age ≥ 18, histologically or cytologically proven SCLC, progressive disease after 1L treatment, and receiving 2L chemotherapy.

Results. A total of 89 patients were assessed in this study. The patients were classified into three groups: 35 patients received the combination of doxorubicin, cyclophosphamide, and vincristine (CAV), 24 patients received single-agent topotecan (TPT), and 30 patients received numerous different treatment schemes. The overall response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), and median overall survival (OS) were 19.1%, 46.1%, 3.5 months, and 6.4 months, respectively. Although no statistically significant difference was found between the three groups in PFS ($p = 0.195$) and OS ($p = 0.286$), there were numerically better outcomes with CAV. In univariate analyses, the comorbidity was related to decreased PFS ($p = 0.044$). However, this relationship could not maintain its statistical significance in multivariate analysis ($p = 0.224$).

Conclusions. It is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC. However, the numerical difference in favor of CAV may be clinically meaningful.

Key words: small-cell lung cancer, second-line, chemotherapy, CAV, topotecan

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Introduction

Lung cancer, divided into two main subtypes based on tumor histology, as non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), is the most common and lethal cancer worldwide [1]. The SCLC, which accounts for approximately 1/7 of lung cancer cases, exhibits a more aggressive course associated with shorter survival [2]. SCLC is generally classified as a limited-stage disease and an extensive-stage disease. The limited disease was characterized by tumors confined to one hemithorax, although local extension and ipsilateral or supraclavicular nodes could also be present, provided they could be encompassed in the same radiation portal as the primary lesion. All other cases were classified as an extensive disease. Approximately two-thirds of patients with SCLC have an extensive-stage disease at initial diagnosis. Although immunotherapy drugs have been added to the current treatment algorithms, conventional chemotherapy still constitutes the

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basis of the treatment of extensive-stage SCLC [3, 4]. Patients with SCLC usually respond to platinum-based treatment in the first-line (1L) setting, with a response rate of 60–70%. However, disease progression is inevitable within one year after the initial treatment in almost all cases, and a second-line (2L) therapy is needed in surviving patients [3, 5].

There are some studies on the efficacy and toxicity of 2L chemotherapy, including many cytotoxic drugs, particularly amrubicin, topotecan (TPT), and irinotecan single-agent regimens, and the combination of cyclophosphamide, doxorubicin, and vincristine (CAV) in patients with SCLC. Among them, TPT is the most often recommended therapy for the 2L treatment in Europe and the United States, however not worldwide [6–11]. As there is no substantial proven superiority between the different treatment regimens, there are no definitive and standard 2L treatment recommendations for patients with SCLC [12–14].

Besides using different chemotherapy regimens, especially the CAV regimen was widely used for many years in our cancer center as a standard 2L treatment in patients with SCLC. Recently, we have started to introduce the single-agent TPT regimen as almost standard in 2L treatment, which is reported to be less toxic than the CAV regimen and stands out in the European and American guidelines. However, in our retrospective observation, we determined that the treatment outcomes of patients who received single-agent TPT were not better than those who received CAV and even had a relatively poorer result. Thereupon, we conducted a study based on this observation.

This study aimed to determine the response rates and survival outcomes obtained with different treatment regimens, the factors affecting the results, and the standard approach in the 2L treatment of patients with extensive-stage SCLC.

Material and methods

This singlecenter, retrospective, cross-sectional, and cohort study was an internal medicine specialty thesis. The inclusion criteria were age ≥ 18, having histologically or cytologically proven SCLC, having progressive disease after 1L treatment of extensive-stage disease, and receiving at least one course of 2L chemotherapy. In this study, medical records of all eligible patients who were treated and followed up in our cancer center between July 2009 and July 2019 were evaluated without any exception. All of the data were meticulously collected and recorded by the thesis assistant, and the data entries were checked and verified one by one by the medical oncologist, the thesis supervisor.

The staging of all patients in this study was determined according to the 7th edition of the American Joint Committee on Cancer staging system. The response evaluation of the patients was done according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The patients who achieved a complete response (CR), partial response (PR), and stable disease (SD) in accordance with RECIST were defined as 'responders'. In contrast, the patients with progressive disease (PD) were identified as 'non-responders'. The disease control rate (DCR) was defined, taking into account all responders, including CR, PR, and SD. However, the overall response rate (ORR) is defined by considering responders, including only CR or PR. The Eastern Cooperative Oncology Group-Performance Score (ECOG-PS) was used to determine the patients' performance status. ECOG-PS ≤ 2 was named 'good performance', whereas ECOG-PS ≥ 3 was called 'poor performance'.

Survival definitions consisted of progression-free survival (PFS) and overall survival (OS). PFS was calculated as (1) the time from the beginning of the 2L treatment to the date of first disease progression despite the 2L treatment (2) the time from the beginning of the 2L treatment to death from any cause in the period of 2L treatment or, (3) the time from the beginning of the 2L treatment to the final visit. Furthermore, OS was calculated as the time from the beginning of the 2L treatment to the date of death or final visit. All patients underwent PFS and OS analysis.

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was required for statistical significance. Primary statistical analysis has included descriptive statistics of the patients including age, gender, smoking history, other comorbid diseases ('positive' means having one or more of the diseases including diabetes mellitus, hypertension, ischemic heart disease, heart failure, arrhythmia, chronic obstructive pulmonary disease, tuberculosis, chronic asthma, chronic renal failure, chronic liver disease, acquired immune deficiency syndrome/AIDS, and secondary malignancy), performance status, the initial stage of the disease, a history of surgery for the primary tumor, a history of the concurrent chemoradiotherapy for the primary tumor, sites of metastasis, and chemotherapy regimens performed in the 1L treatment of extensive-stage SCLC. Descriptive statistics were calculated as proportions and medians. The Kaplan-Meier method was used for survival analysis. Log-Rank analysis was performed to compare the different subgroups. Univariate and multivariate Cox regression analyses were used to identify independent variables.

Results

A total of 89 patients were assessed in this study. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. The baseline demographic and clinical characteristics of the patients

		n, 89	%, 100.0
Age	**years**		
minimum	30.00		
maximum	79.00		
mean	58.03		
Gender			
female		4	4.5
male		85	95.5
Smoking cigarettes			
never		4	4.5
ex-smoker		8	9.0
active-smoker		77	86.5
Comorbidity			
positive		32	36
negative		57	64
Performance status			
ECOG-PS:1–2		76	85.4
ECOG-PS:3–4		13	14.6
Initial stage			
stage I		0	0
stage II		0	0
stage III		11	12.4
stage IV		78	87.6
Surgery for the primary tumour			
yes*		1	1.1
no		88	98.9
Concurrent chemoradiotherapy for the limited-stage disease			
yes		11	12.4
no		78	87.6
Sites of metastasis			
multiple		60	67.4
bone		6	6.7
liver		2	2.2
brain		11	12.4
adrenal		2	2.2
Final status			
died		87	97.8
alive		2	2.2

ECOG-PS — Eastern Cooperative Oncology Group-Performance Score; *Surgery was mainly done for diagnostic purposes

All our patients received 1L chemotherapy for extensive-stage SCLC. It was determined that 71 of the patients (79.8%) received the cisplatin+etoposide (EP) combination, 17 patients (19.1%) received the carboplatin+etoposide combination, and only one patient (1.1%) received the CAV regimen in the 1L treatment. When the responses obtained with 1L treatment were examined, no CR was detected; 60 patients (67.4%) had PR, 18 patients (20.2%) had SD, and 11 patients (12.4%) had PD. With 1L chemotherapy, the DCR was 87.6% and the ORR was 67.4%. Disease progression was detected in all patients despite 1L treatment, and therefore they received 2L chemotherapy.

In the 2L treatment, it was determined that 35 patients (39.3%) received the CAV regimen (doxorubicin, 50 mg/m^2 on day 1, cyclophosphamide, 750 mg/m^2 on day 1, and vincristine, 1.4 mg/m^2 with maximum 2 mg on day 1 every 3 weeks) and 24 patients (27%) received single-agent TPT (4 mg/m^2 intravenously on days 1, 8 and 15 of a 28-day cycle). Moreover, many different treatment schemes were used in the remaining patients (1/3 of all analyzed patients). The study population was classified into three main groups as CAV-treated, TPT-treated, and others. The details of the chemotherapy regimens used in the 2L treatment are shown in Table 2.

An average of 4.2 cycles of chemotherapy was applied in the 2L treatment (range: 1–16 cycles). With the 2L treatment, the ORR was 19.1% for the whole study population, 22.9% for the patients receiving CAV, 16.7% for the patients receiving TPT, and 16.7% for the patients receiving the other chemotherapy regimens. The DCR was 46.1% for the whole study population, 57.1% for the patients receiving CAV, 33.3% for the patients receiving TPT, and 43.3% for the patients receiving the other chemotherapy regimens.

Moreover, with the 2L treatment, the median PFS (mPFS) was 3.5 months for the whole study population (95% Confidence Interval (CI): 2.847 — 4.052), 4.3 months for the patients receiving CAV (95% CI: 3.314–5.294), 2.3 months for the patients receiving TPT (95% CI: 1.347–3.318), and 3.1 for the patients receiving the other chemotherapy regimens (95% CI: 1.995–4.182). Furthermore, the median OS (mOS) was 6.4 months for the whole study population (95% CI: 5.596–7.283), 9.5 months for the patients receiving CAV (95% CI: 6.905–12.084), 5.9 months for the patients receiving TPT (95% CI: 2.904–9.055), and 4.7 months for the patients receiving the other chemotherapy regimens (95% CI: 1.909–7.553). Figure 1 shows the Kaplan-Meier curves for PFS and OS. The details of the outcomes obtained by the 2L treatment are shown in Table 2.

Since the patients who received treatments other than CAV and TPT showed a very heterogeneous distribution, analyses for ORR, DCR, mPFS, and mOS were not performed one by one for each regimen standing in this group.

Table 2. The details of the preferred chemotherapy regimens and the outcomes in the 2L treatment

	n, 89 %, 100.0	
The chemotherapy regimens used in 2L treatment		
group 1: CAV	35	39.3
group 2: TPT	24	27.0
group 3: Others (the following drugs)	30	33.7
cisplatin + etoposide	5	5.6
cisplatin + irinotecan	5	5.6
etoposide + cyclophosphamide	5	5.6
irinotecan	5	5.6
carboplatin + paclitaxel	3	3.4
carboplatin + etoposide	2	2.2
etoposide	2	2.2
capecitabine + temozolomide	1	1.1
gemcitabine	1	1.1
paclitaxel	1	1.1

Responses to 2L treatment

	group 1: CAV, n: 35	group 2: TPT, n: 24	group 3: Others, n: 30
CR	0	0	0
PR	8	4	5
SD	12	4	8
PD	15	16	17
ORR (%)	22.9	16.7	16.7
DCR (%)	57.1	33.3	43.3
mFPS(mo)	4.3	2.3	3.1
mOS (mo)	9.5	5.9	4.7

2L — second-line; CAV — combination of cyclophosphamide; doxorubicin; and vincristine; TPT — topotecan; CR — complete response; PR — partial response; SD — stable disease; PD — progressive disease; ORR — objective response rate; DCR — disease control rate; mPFS — median progression-free survival; mOS — median overall survival; n — number of patients; mo — months

Although the results presented here were numerically different, no statistically significant difference was found in mPFS (p: 0.195) and OS (p: 0.286). Moreover, to clarify the effects of 2L treatment on PFS and OS, analyses were made by dividing the patients into many different groups according to the treatments they received. For example, Group 1 — Arm A: CAV, Arm B: TPT, and Arm C: the others; Group — 2: Arm A: CAV, Arm B: TPT, Arm C: platinum-based and Arm D: the others; Group 3 — Arm A: CAV and Arm B: TPT + irinotecan; Group 4 — Arm A: CAV, Arm-B: topoisomerase inhibitors-based; Group 5 — ArmA: CAV and Arm B: TPT. However, no statistically significant difference was found in all these analyses.

In addition, when we grouped our patients as persons aged over or under 65 years to evaluate the effects of age at the time of diagnosis on survival, there was no statistically significant difference between the two groups. The mPFS was 2.4 months and mOS was 4.7 months in the patients older than 65 years (95% CI for PFS: 0.000—5.219 and 95% CI for OS: 1.538–7.924, respectively, and p = 0.578) whereas mPFS was 3.5 months and mOS was 6.4 months in patients' age equal to or under 65 years (95% CI for PFS: 2.870–4.029 and 95% CI for OS: 4.951–7.928, respectively, and p = 0.696).

A univariate analysis was performed to determine factors affecting survival outcomes — only the presence of other comorbid diseases was associated with decreased PFS (p = 0.044). However, this relationship did not maintain its statistical significance in multivariate analysis (p = 0.224). In addition, no statistically significant difference was found for OS between the groups. The mPFS was 2.9 months and mOS 5.9 months in the patients with the comorbid disease (95% CI for PFS: 1.948–3.769 and 95% CI for OS: 2.883–9.076, respectively) whereas mPFS was 3.8 months and mOS was 6.6 months in

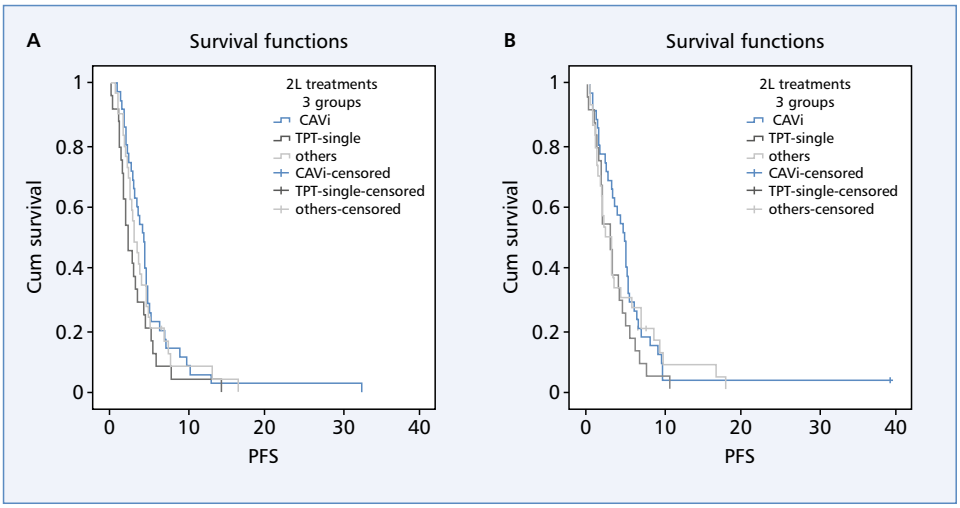

Figure 1. The Kaplan-Meier curves according to 2L chemotherapy regimens; A. For PFS; B. For OS; PFS — progression-free survival; OS — overall survival

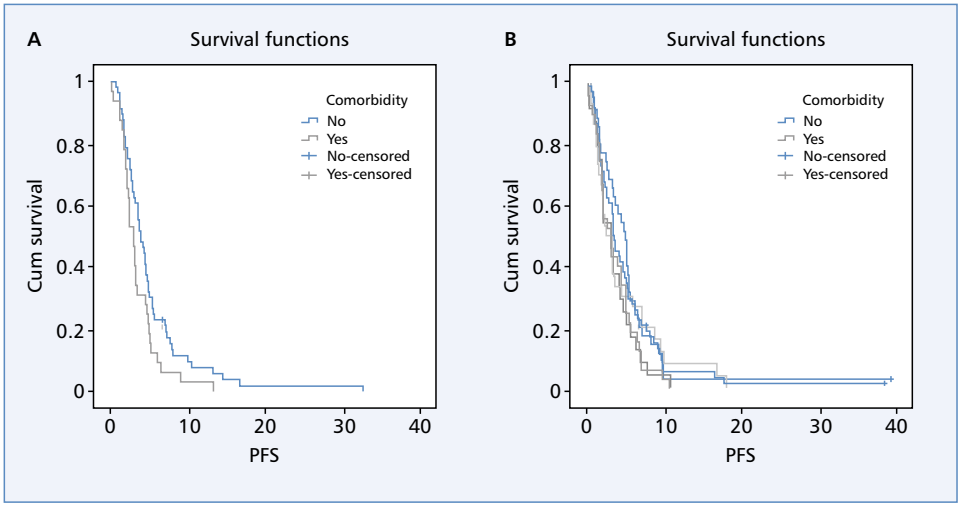

Figure 2. The Kaplan-Meier curves according to comorbidity; **A**. For PFS; **B**. For OS; PFS — progression-free survival; OS — overall survival

the patients without comorbid diseases (95% CI for PFS: 2.964–4.724 and 95% CI for OS: 5.087–8.186, respectively). Figure 2 shows the Kaplan-Meier curves for PFS and OS according to comorbidity.

Although it was determined that 87 of 89 patients (97.8%) had PD despite the 2L treatment, only two patients (2.2%) still did not have PD at the end of the study.

Discussion

SCLC still represents an extremely aggressive disease. Although high response rates are obtained with 1L chemotherapy, almost all extensive-stage SCLC patients would need the 2L treatment within a year [3]. However, there is no 2L treatment recommendation based on sufficiently strong evidence and accepted by all current treatment guidelines [4]. This retrospective study aimed to address the uncertainty on this issue and illuminate the way for clinicians. This study is one of the few studies conducted in the last decade on patients with SCLC who received 2L chemotherapy including CAV regimen. Moreover, this is a critical study because it reveals current real-life data. Furthermore, although this is a singlecenter study, it is valuable as it contains a significant amount of patient data.

This study determined that CAV and TPT regimens were predominantly preferred for 2L therapy in our cohort. It was found that there was a very heterogeneous distribution of treatment preferences in the remaining 1/3 of our patients. The study population was classified into three main groups as CAV-treated, TPT-treated, and others. Since there were very different treatment regimen selections in the last group, as combination regimens including cisplatin + etoposide (EP), carboplatin + etoposide, cyclophosphamide + etoposide, cisplatin + irinotecan, carboplatin + paclitaxel, capecitabine + temozolomide, and as single-agent regimens including irinotecan, etoposide, gemcitabine, and paclitaxel, this group was not heavily addressed in the discussion part of this study. Our discussion was mainly focused on the comparison of CAV and TPT regimens to avoid any bias. There was no statistically significant difference in PFS and OS among the three groups. However, a numerical difference was found, giving the impression that the CAV regimen could produce a survival advantage. Moreover, we determined in our cohort that the presence of other comorbid diseases was associated with shorter PFS. Also, we revealed that age has no prognostic significance.

The standard treatment for patients with extensive-stage SCLC is still chemotherapy, and the treatment is given for palliative purposes. Treatment with cytotoxic drugs has shown developments and changes over the years. In the 1970s, it was demonstrated that the CAV regimen was effective and well-tolerated and was commonly used as a standard 1L treatment [15]. Then, in the 1980s, with the EP regimen, which showed a synergistic effect in preclinical models, it was observed that excellent responses were obtained in limited-stage patients who did not respond to induction chemotherapy with CAV or relapsed after treatment with anthracycline-containing regimens. Thereupon, the EP regimen was increasingly used in the treatment of SCLC [16]. In addition, many previously untreated patients achieved complete responses with the EP regimen, and increased survival was obtained in that way [17]. Studies comparing the EP regimen versus CAV regimen in the 1L treatment reported improved survival and less hematologic toxicity with the EP regimen, making the EP regimen

the most commonly used 1L chemotherapy regimen for extensive-stage SCLC and virtually eliminating the CAV regimen from the 1L treatment [17, 18]. This is still the current situation. When reviewing the treatments our cohort received in the 1L, we detected that almost all patients had received the EP regimen. This result was in agreement with the literature.

Unfortunately, most patients experience disease progression within one year after 1L treatment, and success rates are meager despite 2L treatment [3, 19]. However, unlike the 1L treatment with EP, which has been accepted for almost 40 years, there is still no more standardized 2L treatment protocol. In these patients with relapsed SCLC, in addition to rechallenge therapy with the EP regimen, which has been applied for a long time, CAV regimen or single-agent TPT treatments have also been used frequently, especially in the last two decades. Moreover, apart from these, many different drugs were investigated in the 2L treatment of SCLC [4, 6–11, 16, 20–22]. The most preferred treatment regimens in our cohort were CAV and TPT. Other treatment options, gathered together as a heterogeneous third group, included the treatment options described in the literature. Preferred drug practices in 2L therapy in our cohort were consistent with the current literature.

In the late 1980s, Sculier et al. [22] conducted a phase II study and evaluated the CAV regimen in 2L therapy with a response rate of 13% and median response duration of 26 weeks. Subsequently, two separate comparative studies showed significantly superior results with the CAV regimen compared to oral etoposide, and therefore the studies were interrupted before the planned schedule [23, 24]. About one decade after the article of Sculier et al., von Pawel et al. evaluated the effectiveness of CAV compared to infusional TPT in the 2L treatment of SCLC in a 1:1 randomized, multicenter study including a total of 211 patients. They reported that ORRs were 18.3% and 24.3%, mPFS were 12.3 weeks and 13.3 weeks, and mOS was 24.7 weeks and 25 weeks in patients receiving CAV and TPT, respectively. Moreover, they concluded no statistically significant difference in efficacy between the treatment arms [10]. After that, in the first years of the 21st century, O'Brien et al. conducted a Phase III, multicenter trial comparing supportive care alone with supportive care + oral TPT in the 2L treatment of patients with relapsed SCLC. In this 1:1 randomized study, a total of 141 patients were enrolled, and with oral TPT, the ORR was 7%, and the DCR was 44%, and an mOS with supportive care was 13.9 weeks, and TPT was 25.9 weeks. As a result, they reported a statistically significant prolonged OS with the addition of oral TPT compared to supportive care alone [11]. Later, Eckardt et al. compared the efficacy of oral TPT and infusional TPT in the 2L treatment in a randomized, phase III trial involving a total of 309 patients with SCLC. The rates of ORR were 18.3% with oral TPT and 21.9% with infusional TPT; mOS was 33.0 weeks for oral TPT and 35.0 weeks for infusional TPT. Moreover, the 1- and 2-year survival rates were 32.6% and 12.4% for oral TPT and 29.2% and 7.1% for infusional TPT. Since there was no statistically significant difference between the two groups, they concluded that oral and infusional TPT could be used in the 2L treatment of recurrent SCLC [25]. Although, after these studies, TPT was recommended as the dominant treatment option in the 2L treatment of relapsed SCLC, particularly in Europe and the United States, this suggestion was not adopted worldwide.

Researches continued in many parts of the world due to the lack of strongly recommended 2L standard therapy. In Italy, Garassino et al. conducted a retrospective study in 161 patients with SCLC to evaluate the clinical outcomes of 2L chemotherapy after the initial treatment with EP regimen. In this study, the researchers divided patients into four subgroups by type of 2L treatment: (1) platinum-based rechallenge; (2) anthracycline-based regimens; (3) topotecan; (4) other single agents. They reported that ORR, mPFS, and mOS were 22.9%, 4.3 months, and 5.8 months, respectively. Also, they concluded that there was a statistically significant trend toward higher ORR (34.5% *vs.* 17.5%) and mOS (9.2 months *vs.* 5.8 months) for patients who were rechallenged with platinum-based chemotherapy due to the sensitivity in 1L treatment. Moreover, they offered the platinum-based rechallenge as a standard comparator in future randomized controlled trials of 2L chemotherapy [26]. In a 2:1 randomized, multicenter, phase III trial of amrubicin, a third-generation anthracycline and potent topoisomerase II inhibitor, versus TPT as 2L treatment in a total of 637 patients with SCLC, von Pawel et al. reported that ORR was 31.1% *vs.* 16.9%, mPFS was 4.1 months *vs.* 3.5 months, and mOS was 7.5 months *vs.* 7.8 months, with amrubicin and with TPT, respectively. Moreover, they concluded that amrubicin did not improve survival when compared with TPT [27]. Li et al. conducted a retrospective study in China to compare the effectiveness of 2L treatment versus supportive care and compare the efficacy and safety of different 2L treatment regimens, including etoposide, TPT, irinotecan, and taxanes. A total of 309 patients were evaluated, and 157 received the best supportive care, and the rest of the patients (n = 152) received 2L chemotherapy. The researchers demonstrated that the patients administered 2L chemotherapy lived significantly longer, with a total OS from 1L therapy of 11.5 months compared to 6.0 months in the patients with the best supportive care alone. Also, they reported that the ORR, DCR, mPFS, and mOS were 39.5%, 59.2%, 3.3 months, and 5.3 months, respectively. Moreover, they divided the patients into subgroups by types of 2L

chemotherapy regimens and concluded that there was no statistical difference in ORR, DCR, and mPFS among all of the subgroups, and only treatment with TPT revealed a mild significant mOS advantage [28]. In Japan, Goto et al. compared the combined chemotherapy with cisplatin, etoposide, and irinotecan versus TPT alone as 2L treatment in a multicentre, open-label, randomized phase 3 trial, including 180 patients with relapsed SCLC. The researchers demonstrated a survival advantage of approximately six months favoring the combined chemotherapy arm (18.2 months *vs.* 12.5 months). As a result, they concluded that combination chemotherapy with cisplatin + etoposide + irinotecan could be considered the standard 2L chemotherapy for selected patients with SCLC [14]. Also, the efficiency of different 2L chemotherapy regimens, including irinotecan, TPT, paclitaxel, and docetaxel, was compared in a retrospective analysis of 116 patients with SCLC. The researchers reported that the ORR was 19.05%, DCR was 61.90%, mPFS was 75 days, and mOS was 180 days. Moreover, they showed that paclitaxel achieved the best DCR of 78.57%, while irinotecan achieved the best ORR of 22.22%. Besides, they revealed that patients treated with irinotecan also achieved the best mPFS and mOS of 91 and 595 days, while the mPFS of TPT, paclitaxel, and docetaxel were 74.5, 81, and 50 days respectively, and the mOS of them were 154, 168.5, and 184 days, respectively [29]. In another study, Xing et al. examined 107 SCLC patients to evaluate the efficacy and safety of single-agent irinotecan in the 2L treatment of refractory and relapsed SCLC. They showed that ORR was 16.82%, DCR was 55.14%, mPFS was 3.8 months, and mOS was 8.1 months. Moreover, they concluded that for patients with SCLC, the single-agent irinotecan in the 2L chemotherapy has a certain effect [30].

The results of our study are consistent with the data in the literature we tried to summarize above. Although in the statistical analysis we performed by applying various grouping formations a statistically significant difference was not detected among the groups in terms of survival, this may be due to the small number of our cohort. On the other hand, when viewed numerically, a survival trend in favor of CAV stands out. It can be assumed that the superiority of the CAVi combination regimen over single-agent TPT might be significant once the number of patients was greater. However, considering all these results and current data in the literature, it is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC.

It was suggested that there are some tricks in selecting a 2L treatment to be applied in case of disease progression after 1L treatment. The most important are advanced age, performance status, other comorbid diseases, and side effects due to initial chemotherapy [31]. Although advanced age was suggested as a handicapped situation, Siu et al. evaluated 608 patients with SCLC and demonstrated that age did not matter as a prognostic factor [32]. We found in our study that age has no prognostic significance. Besides, we determined that the presence of other comorbid diseases in our cohort was associated with shorter PFS. Although progression occurred later in the patients without other comorbid diseases, the presence of comorbidity did not have a statistically negative effect on OS in our cohort. Based on these results, it is worth emphasizing that it will not be suitable to decide whether or not to offer a treatment option based on age or comorbidities only.

In addition, when our study was initially designed, we also planned to analyze the adverse events that occurred with 2L treatment regimens. However, while recording the data, it was determined that most of the side effect data were not noted in the patients' files. Furthermore, we were not sure about the adequacy and reliability of the limited number of adverse events recorded. When real-life data are based on the retrospective review of patient records, such deficiencies may be unavoidable. In our opinion, the most important reasons for this undesirable situation are a lack of sufficient time to record treatment-related side effects in complicated outpatient settings. Therefore, side effect data were not analyzed in order to avoid any bias.

The strengths of this study are that it was based on real-life data, data of all eligible patients having the inclusion criteria were recorded without exception, a single person did all data entries with the same care and consistency, and the entries were checked and verified by a second researcher one by one. On the other hand, the weaknesses of this study are that it was a retrospective and single-center study with no randomization including a relatively small number of patients. Moreover, the existence of a heterogeneous third group other than the homogeneous CAV-treated and TPT-treated groups, and the absence of the data including adverse events of the treatments may cause difficulty in formulating final conclusions.

Conclusions

In this study, no statistically significant difference was found in survival outcomes between 2L treatment regimens applied in patients with SCLC. Therefore, it is still impossible to make a standard recommendation for the 2L treatment of patients with SCLC. However, we think that the difference determined numerically in favor of CAV regimen may be significant, and it will be essential to verify these results with prospective, randomized, multicenter studies with larger patient numbers.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical statement

The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee of the university (Local Ethics Committee approval number: 10.05.2019-2019/1849). Since this was a retrospective file screening study, informed consent was not required.

Authors' contributions

All authors contributed significantly to the study from beginning to the end by making essential additives to conception, design, the collection of data, or analysis and interpretation of data, drafting the manuscript, or revising it critically. All authors read and approved the final status of the manuscript.

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REVIEW ARTICLE

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The role of diagnostics and treatment — lung cancer with *ALK* rearrangement

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ABSTRACT

Lung cancer is the most common cause of cancer-related deaths both in Poland and worldwide. Recently, the incidence of lung adenocarcinoma has been increasing and currently it accounts for about 45% of all diagnosed lung cancers. Patients diagnosed with non-squamous non-small cell lung cancer (NSCLC), especially with adenocarcinoma, cancer containing adenocarcinoma component, large cell carcinoma, as well as patients with not otherwise specified (NOS) cancer may benefit from targeted therapy if molecular tests confirm the presence of activating *EGFR* gene mutations, *ALK*, *ROS1* or *NTRK* rearrangement, or *BRAF* gene mutations. The *ALK* gene rearrangement is a positive predictive marker of tyrosine kinase inhibitors (TKIs) effectiveness, which are more effective than standard chemotherapy in this population, are associated with improving the quality of life and also indicate a different, more tolerable toxicity profile. This study presents the diagnostic sequence and registered treatment options for patients with ALK-positive NSCLC.

Key words: non-small cell lung cancer, *ALK*-rearrangement, ALK-TKI, crizotinib, alectinib, brigatinib, ceritinib

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Introduction

Over the past decade, the approach to the diagnosis and treatment of lung cancer has changed significantly. For many years, the division into a small cell (SCLC) and non-small cell lung cancer (NSCLC) was the most important factor in choosing the treatment option, especially in advanced stages. The subtype of non-small cell lung cancer was not significant as it did not affect the chemotherapy (ChT) or radiochemotherapy (RT) regimen used.

The development of molecular biology, identification of activating mutations and major signalling pathways involved in tumorigenesis and progression of NSCLC and the introduction of targeted therapy using tyrosine kinase inhibitors (TKIs) have resulted in radical changes in the principles of lung cancer diagnosis and choice of treatment method [1, 2]. The *ALK* gene rearrangement is found in approximately 3–7% of patients with non-small cell lung cancer. This aberration almost exclusively affects patients with lung adenocarcinoma and more often non-smokers. Patients with *ALK* rearrangement are clinically characterized by involvement of the mediastinal and supraclavicular lymph nodes, the presence of pleural as well as pericardial or peritoneal effusion and a high percentage of central nervous system (CNS) involvement [3].These patients require an individual therapeutic approach and planning of the treatment strategy from the very beginning. At present, several small-molecule ALK-TKIs are registered by the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for systemic treatment in the first and subsequent lines, some of which are also available in Poland as part of the drug program. The sequence of use of individual inhibitors and their activity within the central nervous system is

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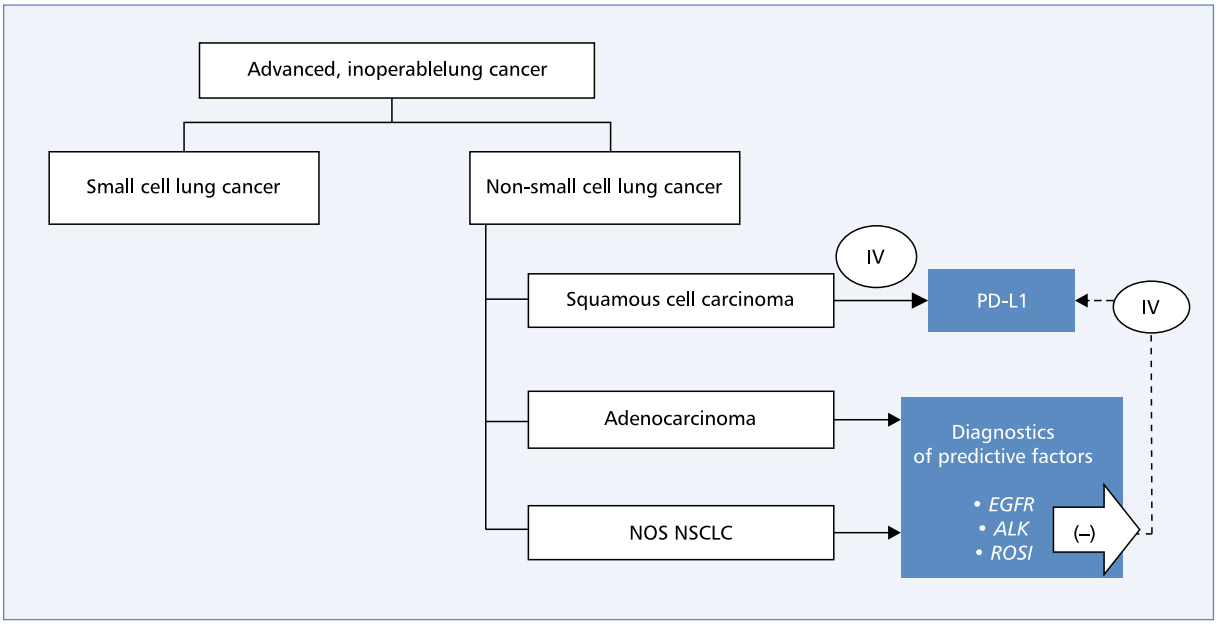

Figure 1. Diagnostic algorithm in advanced, inoperable lung cancer

also important, and the toxicity profile of individual ALK-TKIs should be taken into account.

Morphological diagnostics, assessment of predictive factors in lung cancer

The current diagnostic algorithm strictly depends on disease stage and morphological cancer type. In patients eligible for surgery it is sufficient to determine cancer type (small cell vs non-small cell carcinoma) without specifying the NSCLC subtype. In patients with advanced cancer, accounting for about 80%, it is important not only to determine the NSCLC subtype (squamous cell vs adenocarcinoma) but also to secure the material for predictive factors assessment enabling the selection of patients to appropriate treatment, primarily targeted therapy and immunotherapy [1, 4, 5] (Fig. 1).

The subtype of approximately 70% of NSCLC could be specified based on the morphological features recognized by standard hematoxylin + eosin staining (H+E). In other cases, additional tests are necessary: histochemical (staining for mucin in cancer cells) and immunohistochemical (IHC), which allow the determination of the morphological type of NSCLC [2, 6, 7].

Due to the unique nature of samples, based on which the diagnosis is established (cytological material and/or small, several-millimeter sections), two most sensitive and specific IHC markers are mainly used: thyroid transcription factor-1 (TTF-1) and p40. TTF-1 expression in cancer cells indicates glandular differentiation (GD), whereas p40 is a marker of squamous cell lung cancer. In about 10% of cases, the cancer subtype cannot be determined despite additional tests; this is so-called NOS non-small cell lung cancer [2, 6, 7].

Diagnosis of predictive factors is carried out following a specific algorithm, according to which in patients with locally advanced or generalized adenocarcinoma or NOS, *EGFR* gene mutation is assessed first, then in case of a negative result, *ALK* gene expression and/or rearrangement is assessed, followed by *ROS1* gene rearrangement [1, 3, 4]. In patients with stage IV squamous cell carcinoma or adenocarcinoma and NSCLC-NOS with not confirmed evidence of biomarkers, a predictive IHC test is possible, to assess the expression of PD-L1 protein qualifying for treatment with immune checkpoints inhibitors (so-called immunocompetent drugs) (Fig. 1) [4].

Approximately 10% of patients with adenocarcinoma harbor *EGFR* gene mutation. The presence of *EGFR* mutation in exons 18-21 is an indication for targeted therapy with tyrosine kinase inhibitors already in I line. The basic method used in the diagnosis of *EGFR* gene mutation is the real-time polymerase chain reaction (RT-PCR) technique, characterized by high sensitivity and specificity. It allows detecting genetic aberrations in the hypocellular cell sample containing even ≥ 1% (the minimum number of neoplastic cells required for the diagnosis of EGFR mutation is 100 cells) of cancer cells [1, 4, 5, 8].

In *EGFR*-negative NSCLC the abnormalities in *ALK* gene are assessed in the next step. *ALK* belongs to the insulin receptor tyrosine kinase family, wich is normally expressed in the developing nervous system. In 2007, *ALK* gene rearrangement was found in NSCLC. It results from the fusion of *ALK* and *EML4* genes, which are normally at opposite ends of the same short arm

of chromosome 2p. As a result of intra-chromosomal inversion occurring within the chromosome 2p, both genes fuse and encode fusion protein EML4-ALK, which consequently leads to permanent activation of intracellular signalling pathway, stimulation of tumor cell proliferation and inhibition of apoptosis [4, 9, 10]. In addition to the most common *EML4-ALK* rearrangement in NSCLC, there are also other types of *ALK* gene translocation (*TGF-ALK*, *KIF5B-ALK*, *KLC1-ALK*) that probably do not affect the treatment outcome [9–11].

Aberrations in *ALK* gene are found primarily in patients with adenocarcinoma, often of solid structure or with a signet-ring cell, mucinous or acinar especially cribriform type, less often a papillary component. Patients with confirmed *ALK* gene mutations are usually slightly younger than other NSCLC patients. They are generally non-smokers or light smokers (≤ 10 pack-years) [9, 10].

ALK rearrangement is most commonly considered to be exclusionary for the *EGFR* and *KRAS* mutations, although there is some data indicating possible coexistence of both aberrations.

Until recently, the main validated diagnostic test to detect *ALK* gene rearrangement was the fluorescence in situ hybridization (FISH) method with specially labelled probes. There is a sufficient method, but requiring adequate diagnostic facilities, especially a special fluorescence microscope and qualified staff. In addition, FISH is expensive, difficult to interpret and time-consuming method. Another disadvantage is reaction instability; the signal disappears after some time, precluding reassessment [4, 5, 9, 12].

Currently, the predictive immunohistochemical test with anti-D5F3 antibody is used with very good effects. It is more accessible, cheaper, does not require additional diagnostic facilities, in addition to the standard used in the pathology department [4, 5, 9].

Another, currently required predictive test is the assessment of abnormalities in *ROS1* gene. *ROS1* gene rearrangement is found in about 1–2% of NSCLC patients, non-smokers, mainly with adenocarcinoma. This aberration occurs within the long arm of chromosome 6 (6q22) encoding a protein that functions as a receptor with an intracellular tyrosine kinase domain. Similarly to *ALK* gene, various gene fusions also appear in *ROS1* gene; of these, the *CD74-ROS1* fusion has been reported as the most common [1, 4, 5, 9]. Detection of *ROS1* rearrangement allows the use of crizotinib.

In Poland, the reimbursed method for determining disorders in *ROS1* gene, based on NSCLC treatment program, is FISH method, subjected to the abovementioned limitations.

In the United States and many Western European countries IHC is used as a screening test. Positive results require confirmation by FISH, while negative ones are considered binding [1, 4, 5].

Despite the increasingly widespread next-generation sequencing (NGS) method, which allows the simultaneous detection of many genetic abnormalities, including *EGFR*, *ALK*, and *ROS1* aberrations, monogenic techniques are still widely used worldwide. First of all, this is due to the fact that they are more accessible, faster and less expensive. In addition, NGS results which are questionable or discrepant with clinical data, need to be confirmed by monogenic tests [13].

The first line of systemic treatment with ALK tyrosine kinase inhibitors

Crizotinib was the first small molecule ALK tyrosine kinase inhibitor approved by FDA. It is a first-generation inhibitor, inhibiting not only ALK but also c-MET and ROS1 tyrosine kinase. Its efficacy and safety in the first-line treatment were evaluated in an open-label, multicenter PROFILE 1014 trial [14]. The study enrolled 343 patients with ALK-positive advanced or metastatic non-squamous NSCLC, with no previous systemic treatment. Patients were randomly assigned (1 : 1) to the arm receiving crizotinib 250 mg twice daily until disease progression or unacceptable toxicity (n = 172) or standard first-line chemotherapy (pemetrexed 500 mg/m^2 in combination with a platinum derivative: cisplatin 75 mg/m^2 or carboplatin AUC 5 or 6 mg/mL/min for up to 6 cycles) (n = 171). Patients from chemotherapy arm were permitted to crossover to crizotinib arm at the time of disease progression. Crizotinib has demonstrated superiority over chemotherapy in terms of progression-free survival (PFS). The median PFS was 10.9 months *versus* 7 months, respectively, and the use of crizotinib in first-line treatment reduced the risk of disease progression by as much as 55% compared to chemotherapy (HR 0.45; 95% CI 0.35–0.60; P < 0.001). In addition, a significantly higher response rate (RR) was found in patients receiving crizotinib (74% *vs.* 45%). There was no difference in overall survival (OS), most likely due to the design of the study (crossover): in PROFILE1014, the percentage of patients in chemotherapy arm receiving crizotinib after disease progression was close to 85% [14]. In 2018, the results of the final analysis of crizotinib first-line treatment effect on the overall survival were published. After a median follow-up of 46 months, eliminating the crossover effect using appropriate statistical tools, crizotinib was shown to reduce the risk of death by nearly 65% (mOS 59.8 months for crizotinib versus 19.2 months for chemotherapy, HR 0.346; 95 % CI 0.081–0.718). Therefore, the use of molecularly targeted therapy improves the patients' prognosis from the very beginning of treatment and is more effective than standard first-line chemotherapy [15].

Alectinib is a second-generation ALK-TKI, demonstrating the high intracranial activity, which is very important in ALK-positive lung cancer. The efficacy and safety of this drug in treatment-naive patients with advanced ALK-positive NSCLC was evaluated in ALEX trial and compared directly with the first-generation inhibitor. In total, 303 patients were enrolled to this multicenter, open-label clinical trial, randomly assigned (1: 1) to the arm receiving alectinib 600 mg twice daily (n = 152) or crizotinib 250 mg twice daily (n = 151). After a median follow-up of 17.6 months for crizotinib and 18.6 months for alectinib, disease progression or death was reported in 68% and 41% of patients, respectively. After 12 months, 68.4% of patients in alectinib arm and 48.7% of patients in crizotinib arm were progression-free (HR 0.47; 95% CI 0.34–0.65; P < 0.001). It has been shown statistically and clinically significant prolongation of PFS in patients treated with alectinib by more than 15 months compared to crizotinib. The median PFS was 25.7 months in patients in alectinib arm versus 10.4 months in crizotinib arm (HR 0.50; 95% CI 0.36–0.70; P < 0.001) [16]. The updated PFS results were presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting. The use of alectinib has been shown to reduce the risk of disease progression or death by 57% compared to crizotinib and extend progression-free survival by more than 2 years (median PFS 34.8 months *vs.* 10.0 months for alectinib and crizotinib, respectively, HR 0.43; 95% CI 0.32–0.58) [17]. Overall survival data has not yet matured. According to ALEX trial protocol crossover was not permitted, but some patients treated with crizotinib received alectinib after disease progression as part of another clinical trial or expanded access program (EAP) [16].

Ceritinib is another second-generation ALK inhibitor registered in the first-line treatment. An open, multicenter, phase III phase ASCEND 4 clinical trial enrolled 376 patients with stage IIIB/IV non-squamous NSCLC. Patients were randomly assigned (1: 1) to arm receiving ceritinib 750 mg/day (n = 189) or chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min in combination with pemetrexed 500 mg/m^2 for 4 cycles with the possibility of pemetrexed maintenance treatment) (n = 187). The study showed the superiority of ceritinib over chemotherapy in terms of PFS (median PFS 16.6 months versus 8.1 months, respectively; HR 0.55, 95% CI 0.42–0.73; P < 0.00001). Overall response rate (ORR) was significantly higher in patients treated with ceritinib (72.5% in ceritinib arm *vs.* 26.7% in the chemotherapy arm) [18].

There are also available the preliminary results of phase III ALTA-1L clinical trial, which directly compared the efficacy and safety of the next second-generation ALK inhibitor, brigatinib and the first-generation ALK inhibitor, crizotinib. The study included 275 treatment-naive ALK-positive NSCLC patients, who were randomly assigned (1: 1) to arm receiving brigatinib 180 mg daily (n = 137) or crizotinib 250 mg twice daily (n = 138). PFS was a primary endpoint of the study. Interim analysis performed after a median follow-up of 11 months for brigatinib and 9.3 months for crizotinib showed a significantly increased percentage of progression-free patients after 12 months in brigatinib arm (67% *vs.* 43% in crizotinib arm); HR 0.49; 95% CI 0.33–0.74; P < 0.001). Brigatinib was also superior in terms of ORR (71% *vs.* 60%) and intracranial response rate (78% *vs.* 29%) [19]. Updated ALTA-1L results after a median follow-up of over 2 years indicate that the use of brigatinib is associated with a 57% reduction in disease progression or death risk (HR 0.43, 95% CI 0.31–0.61) compared to crizotinib [20]. Therefore, brigatinib is the next ALK-TKI being more effective than crizotinib in first-line treatment. In February this year, EMA issued a positive recommendation regarding the use of brigatinib in the first-line treatment; the drug is awaiting FDA registration in this indication.

An open, randomized phase III clinical trial is currently ongoing that directly compares the efficacy and safety of crizotinib and lorlatinib in treatment-naive patients with ALK-positive advanced lung cancer [21]. Lorlatinib is a third-generation ALK-TKI that is effective against the largest number of different resistance mutations resulting from treatment with lower generation ALK-TKIs.

The second and subsequent lines of systemic treatment with ALK tyrosine kinase inhibitors

In patients with *ALK*-rearranged NSCLC the use of ALK-TKI in the first line of treatment is of key importance. Otherwise, when the material for *ALK* gene rearrangement determination is not available or patient needs to immediately initiate the treatment due to the deteriorating general condition, it is necessary to pursue toward tissue specimen collection and testing molecular disorders before qualifying for the next line treatment.

The efficacy and safety of crizotinib in the treatment of patients with advanced or metastatic *ALK*-rearranged NSCLC after the failure of a prior platinum-based therapy was evaluated in a multicenter, open-label phase III PROFILE 1007 study. Patients were randomly assigned (1: 1) to the arm receiving crizotinib 250 mg twice daily or standard second-line chemotherapy (docetaxel 75 mg/m^2 intravenously every 3 weeks or pemetrexed 500 mg/m^2 intravenously every 3 weeks in patients with non-squamous NSCLC). The primary endpoint of the study was PFS. A statistically and clinically significant benefit has been demonstrated with crizotinib compared to second-line chemotherapy. The median PFS was 7.7 months and 3 months, respectively (HR 0.49;

95% CI 0.37–0.64; P < 0.001), and the response rate was 65% and 20%, respectively (P < 0.001). The study did not show any benefits in terms of OS, probably due to the possibility of crossover of patients from chemotherapy to crizotinib arm at the time of disease progression) [22].

In patients with disease progression during crizotinib treatment, the next-generation ALK-TKIs are more effective than chemotherapy. The effectiveness of alectinib in sequential treatment has already been confirmed in phase II single arm clinical trial with ORR as the primary endpoint (48%) [23]. The superiority of alectinib over chemotherapy in patients with crizotinib resistance was confirmed in a multicenter, open-label, phase III ALUR study involving 107 patients. Prior use of one line of systemic chemotherapy was permitted. Patients were randomly assigned (2 : 1) to the arm receiving alectinib 600 mg twice daily (n = 72) or investigator's choice chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 intravenously every 3 weeks) (n = 35). PFS, the primary endpoint of the study, was statistically prolonged in the alectinib arm compared to chemotherapy arm (mPFS 9.6 versus 1.4 months, respectively; HR 0.15; 95% CI 0.08–0.29; P < 0.001). The response rate in patients receiving alectinib was 37.5%, while in patients treated with chemotherapy only 2.9% [24].

Brigatinib was another inhibitor whose efficacy and safety was assessed in patients with disease progression during treatment with crizotinib. In total, 222 patients after prior chemotherapy (regardless of the number of treatment lines) were included in the multicenter, open-label, phase II ALTA clinical trial/ They were randomly assigned to the arm receiving brigatinib 90 mg daily (arm A, n = 112) or brigatinib 180 mg daily, after an initial 7-day treatment with a loading dose of 90 mg/day (arm B, n = 110). ORR, the primary endpoint of the study, was 45% for 90 mg dose and 54% for 180 mg dose, respectively. PFS was one of the secondary endpoints, with a median of 9.2 months and 12.9 months for lower and higher dose of brigatinib, respectively. The daily dose of 180 mg was determined to be assessed in further clinical studies [24]. In 2020, updated results of the ALTA clinical trial were published after a median follow-up of 19.6 months for Arm A and 24.3 months for Arm B. The median PFS was 9.2 months versus 16.7 months for arms A and B, respectively, while median OS was 29.5 months versus 34.1 months for patients receiving brigatinib 90 mg and 180 mg, respectively [26]. The effectiveness of ceritinib sequential treatment was evaluated in a multicenter, randomized, open-label, phase III ASCEND 5 clinical trial, which included 231 patients with stage IIIB/IV ALK-positive NSCLC. Patients enrolled in the study had to have disease progression during or after treatment with one or two lines of chemotherapy, and progression during crizotinib treatment. Patients were randomly assigned (1 : 1) to the arm receiving ceritinib 750 mg/day on an empty stomach (n = 115) or pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2 (n = 116). The primary endpoint of the study was PFS, and secondary endpoints included OS, objective response rate and intracranial response rate. The use of ceritinib was associated with a 51% reduction in the risk of disease progression (median PFS 5.4 months for ceritinib and 1.6 months for chemotherapy, HR 0.49; 95% CI 0.36–0.67; P < 0.0001). There was also a huge difference in terms of response rate: 39.1% and 6.9%, respectively. Despite its high effectiveness, ceritinib is unfortunately characterized by an unfavorable toxicity profile [27].

The efficacy and safety of treatment with third-generation ALK inhibitor lorlatinib was assessed in phase II clinical trial in which patients were assigned to six cohorts: EXP1 — treatment-naive patients, EXP2 — patients with disease progression after treatment with crizotinib only, EXP3A — patients with disease progression after treatment with crizotinib and one or two chemotherapy lines used before or after crizotinib, EXP3B — patients with disease progression after treatment with crizotinib and one other ALK-TKI and any number of chemotherapy lines, EXP4 — patients with disease progression after treatment with two ALK-TKIs, and EXP5 — patients with disease progression after treatment with three ALK-TKIs. Patients who previously received at least one ALK-TKI (EXP2-5) had an ORR of 47% and an intracranial response rate of 63%. In patients who were treated with one ALK-TKI — crizotinib (EXP2-3A), the ORR was 69.5%, while in patients treated with crizotinib and one or two/more other ALK-TKIs, the ORR was 32.1% and 38.7%, respectively (mPFS 6.9 months) [28]. The available ALK TKI and their pivotal trials are summarized in Table 1.

The intracranial activity of small molecule ALK tyrosine kinase inhibitors

About 40% of patients with *ALK*-rearranged NSCLC have metastases in the central nervous system (CNS) at the time of initial diagnosis. ALK-positive lung cancers show some kind of neurotropism, which is probably associated with the role-playing by ALK protein in the development of the nervous system [29].

In more than 30% of patients treated with crizotinib, the disease progresses within 12 months of starting treatment, and the most common location for the progressing or new metastatic lesions are the central nervous system. In the ALEX clinical trial, the high intracranial activity of alectinib was noteworthy. At the time of enrollment, central nervous system metastases occurred in 42% of patients in alectinib arm and 38% of patients in crizotinib arm. It was shown that the time to progression of metastases in the central nervous system was significantly

Table 1. Available ALK TKI and pivotal trials (proszę o podanie odnośnika w tekście)

Drug	Trial	Primary endpoint	Control arm	FDA/EMA registration
First-line treatment				
Crizotinib	PROFILE 1014 [14, 15]	mPFS 10.9 *vs.* 7.0 months Hr 0.45. P < 0.001 95% CI 0.35–0.60 MOS 59.8 *vs.* 19.2 months HR 0.346; 95% CI 0.081–0.718)	Cisplatin/carboplatin + pemetrexed	2011/22.10.2015
Ceritinib	ASCEND 4 [18]	mPFS 16.6 *vs.* 8.1 months HR 0.55. P < 0.00001 95% CI 0.42–0.73	Platinum-based cht	26.05.2017/18.05.2017
Brigatinib	ALTA-1L [19, 20]	12-miesięczny PFS 67% *vs*. 43% HR 0.49. P < 0.001 95% CI 0.33–0.74 *HR dla PFS 0.43 95% CI 0.31–0.61	Crizotinib	
Alectinib	ALEX [17]	mPFS 34.8 *vs*. 10.0 months HR 0.43; 95% CI 0.32–0.58)	Crizotinib	6.11.2017/12.10.2017
Subsequent treatment lines				
Crizotinib	PROFILE 1007 [22]	mPFS 7.7 *vs.* 3.0 months HR 0.49. P < 0.001 95% CI 0.37–0.64	Docetaxel/pemetrexed Second-line treatment after failure of platinum-based CHT	2011/19.07.2012
Ceritinib	ASCEND 5 [27]	mPFS 5.4 *vs.* 1.6 months HR 0.49. P < 0.0001 95% CI 0.36–0.67	Docetaxel/pemetrexed Progression after one or two cht lines and crizotinib	29.04.2014/26.02.2015
Brigatinib	ALTA [26]	ORR 45% *vs.* 54% mPFS 9.2 *vs.* 12.9 months	90 mg/day *vs.* 180 mg/day Progression after any number of cht lines and crizotinib	28.04.2017/20.09.2018
Alectinib	ALUR [24]	mPFS 9.6 *vs*. 1.4 months HR 0.15. P < 0.001 95% CI 0.08–0.29	Docetaxel/pemetrexed Progression after one cht line and crizotinib	11.12.2015/15.12.2016

CI — confidential interval; CHT — chemotherapy; HR — hazard ratio; mPFS — median progression-free survival; ORR — overall response rate

longer in patients receiving alectinib. The cumulative risk of progression or new metastatic lesions in the central nervous system after 12 months of ALK TKI treatment was 41.4% for crizotinib and 9.4% for alectinib and is, therefore, more than four times lower in patients receiving second-generation inhibitor [16]. The median PFS for patients with metastatic lesions in the central nervous system was 27.7 months in alectinib arm and 7.4 months in crizotinib arm (HR 0.35) [17]. Alectinib has a lower molecular weight than crizotinib. The alectinib molecule is more lipophilic, more easily crosses the blood-brain barrier, moreover it is not a substrate for p-glycoprotein (P-gp), which allows achieving a higher concentration in the cerebrospinal fluid (CSF) [29].

The updated results of ALTA-1L clinical trial after a median follow-up of over 2 years also indicate that the use of brigatinib in patients with metastatic lesions in the central nervous system at baseline is associated with a reduction in the risk of disease progression or death by 76% compared to crizotinib (HR 0.24, 95% CI 0.12–0.45) [20]. In patients receiving brigatinib after disease progression during crizotinib treatment, the intracranial response rate was 50% and 67% in patients receiving the lower (90 mg) and higher dose of brigatinib (180 mg), respectively. The median duration of intracranial response in these patients was 9.4 months and 16.6 months, respectively [26]. Patients treated with ceritinib in first-line also had a significantly higher intracranial response rate com-

pared to standard platinum-based chemotherapy (72.7% *vs.* 27.3%) [18]. For lorlatinib, the rates of intracranial responses were 87% and 53.1% for the EXP2-3A and EXP4-5 cohorts, respectively [28].

At present, in patients with asymptomatic metastases in the central nervous system, it is recommended to start treatment with next-generation small-molecule ALK tyrosine kinase inhibitors that penetrate the central nervous system. In patients with isolated asymptomatic progression in the central nervous system treated with crizotinib it is recommended to switch the therapy to an inhibitor with high activity in CNS, thus postponing brain radiotherapy [29]. The intracranial activities of individual ALK inhibitors are described in Table 2.

The sequence of treatment with ALK tyrosine kinase inhibitors

The validity of the concept of sequential treatment with ALK-TKIs was confirmed in the French retrospective IFCT-1302 CLINALK clinical study. The analysis included data from 318 ALK-positive NSCLC patients who received crizotinib as part of the EAP after drug registration. Among others, a multivariable OS analysis was performed in patients treated with crizotinib as the first ALK inhibitor, followed by treatment with next-generation inhibitors after disease progression (n = 84, 32%). It was demonstrated that in patients who received next-generation inhibitors after disease progression, the median OS was 25 months, e.g. up to 89.6 months from diagnosis of metastatic lung cancer and was significantly longer than in patients receiving chemotherapy or only the best supportive care (BSC) after progression during crizotinib treatment. However, researchers point out that among patients with disease progression during crizotinib treatment only 60% received any treatment, while next-generation inhibitors were used only in 32% of patients [30]. This was most often due to the disease-related deterioration of patients performance status (PS) and dynamically progressing lesion(s) within the central nervous system. Therefore, and in view of the latest data from clinical trials, it seems reasonable to start therapy with an inhibitor showing high activity within CNS. The use of alectinib in first-line treatment is associated with PFS improvement by more than 24 months (34.8 months *vs.* 10 months) compared to crizotinib in first-line [16]. Similarly, the use of brigatinib in first-line treatment reduces the risk of disease progression or death by 57% compared to crizotinib with OS prolongation by more than 4 months (mOS 29.5 months *vs.* 34.1 months) [19]. It is extremely important to postpone radiotherapy of the central nervous system in patients who are mostly younger, professionally, family and socially active. In the case of disease progression during the treatment with second-generation ALK-TKI, third-generation ALK-TKI lorlatinib can be used, whose activity covers the largest spectrum of secondary resistance mutations to lower generation ALK-TKIs.

Side effects of ALK tyrosine kinase inhibitors

ALK-TKIs have a different toxicity profile than chemotherapy. The most common adverse reactions

Table 2. ALK TKIs activity in the central nervous system

First-line treatment with ALK TKI		ALK TKIs in second and subsequent treatment lines (after failure of other ALK TKIs)	
CRYZOTINIB			
PROFILE1014 [14]	icORR 50% icDOR 5.5 months		
CERITINIB			
ASCEND-4 [18]	icORR 73% icDOR 16.6 months	ASCEND-5 [27]	icORR 35% icDOR 6.9 months
ALECTINIB			
ALEX [16]	icORR 81% icDOR 17.3 months	ALUR [24]	icORR 54%
BRIGATINIB			
ALTA-1L [20]	icORR 83% icDOR NR HR dla PFS 0.24	ALTA 180 mg [26]	icORR 67% icDOR 16.6 months

ALK TKI — ALK tyrosine kinase inhibitor; icORR — intracranial overall response rate; icDOR — intracranial duration of response; NR — not reached; HR — hazard ratio; PFS — progression-free survival

Table 3. Adverse events of ALK tyrosine kinase inhibitors [32–34]

	CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
Grade G3 adverse events in > 5% of patients	↑ AST/ALT 14% ↓ ANC 11%	↑ ALT 31% ↑ GGT 29% ↑ ALP 29% ↑ AST 17% diarrhea 5% vomitus 5%	↑ ALT 5% ↑ AST 5%	↑ CPK 16% ↑ lipase 13% hypertension 10% ↑ amylase 5%	↑ cholesterol 18% ↑ triglycerides 18% ↑ lipase 10% dyspnea 5,4%
SAE	38%	41%	26%	41%	32%
Respiratory complications	10.5%	14.7%	5.9%	13.5%	7.5%
Characteristic adverse events	visual disturbances (flashes, light columns, blurred vision) NEUTROPENIA	gastrointestinal disorders (diarrhea, abdominal pain, nausea, vomiting)	Anemia	ILD, hypertension	Mental disorders, mood, speech and sleep disorders
The need to reduce the dose	21%	80%	16%	29%	22%
Molecular target	ALK ROS1 MET/HGF	ALK IGF-1	ALK	ALK EGFR	ALK ROS1 MET/HGF

ALK — anaplastic lymphoma kinase; ALP — alkaline phosphatase; ALT — alanine aminotransferase; ANC — absolute neutrophil count; AST — asparaginian aminotransferase; CPK — creatine phosphokinase; EGFR — epidermal growth factor receptor; GGT — gamma-glutamyl transpeptidase; HGF — hepatocyte growth factor; IGF-1 — insulinę growth factor; ILD — intestinal lung disease; SAE — serious adverse even

of crizotinib reported in at least 5% of patients in the PROFILE 1007 clinical trial included visual disturbances, like visual acuity impairment or blurred vision, as well as diarrhea, nausea, vomiting, constipation, elevated liver enzymes, peripheral edema, dysgeusia (taste disturbance), dizziness or upper respiratory tract infection. Most side effects were mild to moderate in severity and transient in nature as well manageable. The most common side effects of chemotherapy were fatigue, alopecia, shortness of breath and rash [22]. In the PROFILE 1014 clinical trial, the most common adverse reactions in the crizotinib arm included, as in the PROFILE 1007 study, visual disturbances, diarrhea and edema, while in the chemotherapy arm fatigue, anemia and neutropenia [14]. The percentage of adverse effects of alectinib and crizotinib in the ALEX clinical study was similar in both arms, while both inhibitors differed significantly in the toxicity profile. Adverse reactions more commonly seen in the alectinib group were anemia (20% *vs.* 5% in crizotinib arm), myalgia (16% *vs.* 1%), elevated bilirubin level (15% *vs.* 1%), weight gain (10% *vs.* 1%), musculoskeletal pain (7% *vs.* 2%) and photosensitivity reactions (5% versus 0%). In contrast, side effects more commonly seen in patients receiving crizotinib included nausea (48% *vs.* 14% in alectinib arm), diarrhea (45% *vs.* 12%), and vomiting (38% *vs.* 7%). Grade 3–5 adverse reactions were more common in the crizotinib arm (41% for alectinib and 50% for crizotinib, respectively) so that alectinib appears to be a safer drug [16]. In the case of brigatinib, the percentage of adverse reactions in the form of interstitial pneumonia in patients using the dose of 180 mg was successfully reduced by introducing 7-days treatment with a loading dose of 90 mg [26]. Ceritinib appears to have the least favorable toxicity profile. The most common side effects of ceritinib reported in ASCEND-4 clinical trial included diarrhea, which occurred in up to 85% of patients, nausea (69%), vomiting (66%), and elevated alanine aminotransferase level (60%). The most common chemotherapy side effects were nausea and vomiting, but they were less common than in patients treated with ceritinib (55% *vs.* 36%, respectively), and anemia (35%) [18]. In the ASCEND-5 clinical trial, adverse events that were significantly more common in ceritinib arm than in chemotherapy arm were diarrhea (up to 72% *vs.* 18%, respectively), nausea (66% *vs.* 24%), vomiting (52% *vs.* 5%), elevated alanine aminotransferase (43% *vs.* 9%) and aspartate aminotransferase level (37% *vs.* 5%). At least one dose reduction due to adverse reactions was required in 61% of patients in ceritinib arm and 18% of patients receiving pemetrexed and 26% of patients receiving docetaxel [27]. The incidence and intensity of gastrointestinal adverse reactions quite significantly hindered the widespread use of ceritinib at a dose of 750 mg daily (ASCEND-4 and ASCEND-5 clinical studies). The phase I ASCEND-8 clinical trial compared the pharmacokinetics and frequency of adverse reactions of ceritinib 450 mg daily and 600 mg daily taken with a low-fat meal and ceritinib 750 mg daily taken fasting. Ceritinib 450 mg daily with a low-fat meal and 750 mg taken fasting has been shown to have similar pharmacokinetics, but 450 mg daily was associated with fewer

side effects. Diarrhea was found in 43% of patients, nausea in nearly 30% of patients and vomiting in over 18% of patients. The gastrointestinal side effects were mild (mainly grade 1), no grade 3 or 4 side effects or no serious side effects were reported. No patient discontinued the treatment due to gastrointestinal adverse reactions [31]. The currently recommended dose of ceritinib is 450 mg daily taken with a low-fat meal.

Although ALK-TKI treatment is better tolerated than chemotherapy, the toxicity profile of individual inhibitors varies. The most characteristic adverse effects of different ALK TKI are summarized in Table 3.

Possibilities of using ALK-TKI in Poland

In Poland, patients are qualified for ALK TKI treatment in accordance with the criteria of Drug Program (Appendix B6 — treatment of non-small cell lung cancer). As part of the first-line treatment of patients who have not received prior systemic therapy, a first-generation inhibitor, crizotinib and two second-generation inhibitors, alectinib and ceritinib are available. Crizotinib can also be used in a patient with *ALK* gene rearrangement and disease progression after one or two lines of chemotherapy. Treatment with alectinib or ceritinib is also possible when other ALK TKI treatment fails (including failure of crizotinib treatment). The basic qualification criterion for ALK TKI treatment is confirmation of *ALK* gene rearrangement (by immunohistochemistry [IHC], which does not require further confirmation by fluorescence in situ hybridization [FISH] or next-generation sequencing [NGS]). This molecular aberration should be sought in patients diagnosed with adenocarcinoma or NSCLC with a predominance of this histological subtype. In the case of alectinib treatment, this group should also include patients with a diagnosis of large cell carcinoma or NOS NSCLC. As part of the drug program, it is possible to use ALK TKIs in patients with metastatic lesions within the central nervous system. The prerequisite for this is no signs of progression after local treatment (neurosurgery or irradiation), no clinically significant neurological symptoms, and no need to increase glucocorticoid doses within a month before starting ALK TKI treatment. Alectinib, which is highly active within the central nervous system, can be used in systemic treatment in patients who have not received prior local treatment. The condition for this is also the absence of clinically significant neurological symptoms resulting from CNS involvement.

Treatment with ALK TKI is continued until disease progression or unacceptable toxicity. The effectiveness of treatment is determined based on imaging tests and according to the RECIST 1.1 criteria every 3 months and treatment toxicity based on laboratory tests performed every 4 weeks. For alectinib, it is important to monitor the phosphocreatine kinase level (every 2 weeks in the first month of treatment, then every 4 weeks or as clinically indicated) [35].

Summary

Introduction of ALK-TKI treatment improved the prognosis of patients with ALK-positive NSCLC. Several medications of this group are currently registered and reimbursed. For first-line treatment, both first-generation (crizotinib) and second-generation inhibitors (alectinib and ceritinib) are available. Another second-generation ALK-TKI, brigatinib is awaiting registration and reimbursement. Due to higher activity in the central nervous system and longer time to disease progression, it is recommended to start therapy with a second-generation inhibitor. In case of disease progression during crizotinib treatment, two second-generation inhibitors are available for sequential treatment (alectinib or ceritinib). To make the use of ALK-TKI possible, molecular diagnostics and confirmation of *ALK* gene rearrangement play a key role, and thus the availability of an adequate amount of good-quality tissue material for these tests.

Conflicts of interest

The authors declare to have no conflict of interest.

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REVIEW ARTICLE

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Desensitization in patients hypersensitive to platinum compounds in gynecologic oncology

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ABSTRACT

The treatment of ovarian cancer based on platinum analogs has taken on a new and additional importance in recent years. The introduction of modern maintenance therapy — PARP inhibitors — has significantly prolonged the time to progression in recurrent and newly diagnosed ovarian cancer and clinically meaningful, as per SOLO-2 results, prolonging overall survival in recurrent disease. This is an absolute breakthrough in the treatment of advanced forms of this cancer. Sensitivity to platinum is a prerequisite for the efficacy of this therapy as well as patient eligibility for treatment. Hypersensitivity issues can significantly limit access to this modern and effective maintenance therapy. Platinum hypersensitivity usually occurs in subsequent lines of therapy and with subsequent cycles of treatment. Hypersensitivity reactions cannot always be predicted, despite known risk factors. In order to maintain platinum-based treatment, we can modify premedication modalities, but appropriate desensitization protocols seem to be most effective. This article describes the most commonly used desensitization methods in patients with ovarian cancer and platinum hypersensitivity in a practical way, e.g., as they are used in the centers where the authors of this publication practice.

Key words: ovarian cancer, platinum, carboplatin hypersensitivity, desensitization, PARP inhibitors

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Introduction

The change that has occurred in the treatment of ovarian cancer in recent years is related to the introduction of PARP inhibitors into its treatment. These drugs used as maintenance treatment after first-line response and after relapse significantly prolonged the time to progression [1–4], and in the case of olaparib as maintenance treatment after relapse, clinically meaningful prolonged lifetime [5].

The use of PARP inhibitors as maintenance treatment requires a response to treatment with platinum derivatives. Maintaining platinum treatment is particularly important because of that. The fairly common phenomenon of hypersensitivity to platinum often results in abandoning treatment with these cytostatic agents. This can be prevented by desensitization procedures, which allows the continuation of therapy and, in some ovarian cancer patients, the inclusion of maintenance treatment with PARP inhibitors.

Hypersensitivity to platinum compounds — incidence and risk factors

Drug hypersensitivity reactions (DHRs) include all drug reactions that clinically resemble allergic reactions. They are difficult to predict, vary in severity, and can be life-threatening to the patient, thus requiring

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a change in therapy. It is estimated that DHRs account for 15% of all adverse drug reactions (ADRs) and affect approximately 7% of the general population [6]. Hypersensitivity reactions are mostly caused by common drugs (antibiotics and non-steroidal anti-inflammatory drugs), but they can be caused by any drug [7].

Most commonly, among anticancer drugs, sensitization reactions are caused mainly by platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), L-asparaginase, epipodophyllotoxins (teniposide, etoposide), monoclonal antibodies, procarbazine, and to a lesser extent, 6-mercaptopurine [7–11].

Carboplatin is estimated to cause approximately 0.73% of all reactions induced by intravenous chemotherapeutics and 50% of reactions induced by platinum compounds [12]. Hypersenitivity reactions are found in 1–44% of patients treated with carboplatin and in 5–20% of those treated with cisplatin [13]. The incidence of hypersensitivity reactions to platinum compounds administered in gynecologic oncology has been no higher than in the treatment of other cancers [14]. Their incidence is also not dependent on the route of administration [15, 16], but occurs more frequently with combination therapy, especially in therapy that is the gold standard for ovarian cancer treatment [17].

The CALYPSO trial found that hypersensitivity reactions were more common in those receiving carboplatin with paclitaxel than in those receiving carboplatin with doxorubicin (18.8% *vs.* 5.6%) [18, 19]. Another study also showed higher incidence of hypersensitivity reactions during carboplatin monotherapy than during therapy with pegylated liposomal doxorubicin plus carboplatin (30% *vs.* 0%) [17].

A characteristic feature of hypersensitivity reactions to platinum compounds is that they occur only after administering several therapy cycles (usually after 8 cycles in the case of carboplatin), indicating the importance of the overall amount of the drug that has been administered. Reactions to carboplatin occur in less than 1% of those receiving 1–5 cycles, in 6.5% receiving 6 cycles, in 27% receiving 7 or more cycles, and in nearly 44% receiving third-line therapy [20–24]. Similar observations were also made during cisplatin therapy. Half of the hypersensitivity reactions are of moderate to severe severity [21].

Risk factors for hypersensitivity reactions to platinum compounds include:
— age of less than 70 years [19];
— female sex [13];
— allergy to environmental factors or medications [25, 26];
— severe atopic disease [27];
— mastocytosis [27];
— chronic respiratory and cardiovascular diseases [27, 28];
— taking β-adrenergic blockers and angiotensin-converting enzyme inhibitors [27, 28];
— receiving a single dose of carboplatin of more than 650 mg [24] or a total dose greater than 8000 mg [29];
— length of drug interruption (varying according to different authors: more than 12 months [30], 13 months [24], or 2 years [26]). Schwartz et al. found, for example, that the risk of a severe hypersensitivity reaction during carboplatin administration was 47% when the time elapsed between the last administration of the drug in the first line of treatment and the first in the second line was more than 24 months, and 6.5% when it was less than 12 months [30].

The outcomes of studies evaluating the effect *BRCA1/2* gene mutation presence on hypersensitivity reactions to platinum compounds are conflicting (Tab. 1 [29, 31–33]).

Mechanisms of hypersensitivity reactions to platinum compounds

Both immune and non-immune mechanisms may underlie hypersensitivity reactions to drugs, including platinum compounds. The underlying factor in drug allergy is recognition of drugs or their metabolites by antibodies or activated T lymphocytes.

The second group includes, for example, reactions caused by non-immune mast cell and basophil degranulation or complement activation by drug [6].

Currently the most widely used hypersensitivity reaction classification is based on the time of symptoms onset as a main criteria. According to the classification, drug hypersensitivity reactions are divided into immediate and non-immediate reactions [6, 34–36] (Tab. 2).

CTCAE (Common Terminology Criteria for Adverse Events), ver 5.0 [37] criteria are used to assess the severity of hypersensitivity reactions (Tab. 3).

About half of the hypersensitivity reactions to platinum compounds are of moderate to severe severity, i.e., grade 2 to 3 according to the CTCAE. In a study by Garcia et al. involving a group of 62 patients receiving chemotherapy with platinum compounds, there were 11 grade 1 reactions (all in patients with mutations in

Table 1. Frequency of hypersensitivity reactions to platinum compounds among patients with and without *BRCA1/2* gene mutations

Study	Patients with *BRCA1/2* mutation (%) n	Patients without the mutation (%) n
Moon et al. [29]	(79.3%) 29	(50%) 58
Altwerger et al. [30]	(77.5%) 40	(39.2%) 51
Garcia et al. [28]	(30.8%) 13	(44.9%) 49
Jerzak et al. [31]	(5.4%) 37	(11%) 84

Table 2. Types of drugs hypersensitivity reactions [6, 33–35]

Type of reaction	Time of occurrence	Resistance	Symptoms
Immediate	Within 1–6 hours of drug administration. The faster a reaction develops, the more severe the symptoms	In the case of the allergic mechanism, they are triggered by the presence of specific IgE (type I according to Gell and Coombs), formed upon repeated exposure to a given drug	In 90% of patients: skin and mucosal symptoms (urticaria, angioedema, conjunctivitis, rhinitis). In 40% of patients: bronchospasm. In 30–35% of patients: defense of blood pressure. Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain) are also developed. The most serious symptom is anaphylactic shock: cardiovascular failure that can lead to death. Mild reactions usually resolve with administration of antihistamines and corticosteroids
Not immediate	More than an hour after the drug was administered	Allergic reactions are mediated by T lymphocytes	A variety of skin manifestations are most commonly found, such as maculopapular rashes, delayed urticaria, and persistent erythema. Organ manifestations such as hepatitis, renal failure, interstitial lung disease, anemia, neutropenia, and thrombocytopenia may also occur

Table 3. Classification of the severity of hypersensitivity reactions according to CTCAE

Grade	Symptoms
1	Mild and transient; it is not necessary to discontinue the drug or institute additional therapy
2	Moderate intensity; the medication should be discontinued, but symptomatic treatment (e.g., antihistamines and corticosteroids) results in rapid improvement (administered no longer than 24 hours)
3	Significant intensity, but not immediately life-threatening; symptoms do not resolve quickly enough after symptomatic treatment or discontinuation of therapy or occur after temporary improvement. Hospitalization is recommended
4	Life-threatening. Immediate intervention is recommended
5	Death

BRCA1 or *BRCA2* genes), 14 grade 2 reactions, and 16 grade 3 reactions (all in patients without mutations in *BRCA1* or *BRCA2* genes) [29]. No grade 4 or 5 reactions were reported in this study, but fatal cases have been reported in the literature [38, 39].

Prevention of hypersensitivity reactions to platinum compounds

Before administering platinum compounds, an analysis of the patient's risk of hypersensitivity reactions should be performed, taking into account the factors mentioned earlier. Special caution is recommended for patients who are receiving the 8th cycle of carboplatin or the 2nd cycle for treatment of relapse.

Premedication with antihistamines and corticosteroids is not sufficient to prevent IgE-dependent hypersensitivity reactions, and therefore it is not recommended for standard administration before platinum compounds [40–42]. Some authors suggest including such treatment in patients who have already received 8 cycles of treatment but have not yet experienced a hypersensitivity reaction. One study also found that slower administration of carboplatin with premedication (3 hours instead of the standard half an hour) significantly reduced the rate of hypersensitivity reactions from 21% to 3.4% [43].

When a hypersensitivity reaction occurs, it is crucial to recognize it as soon as possible and implement appropriate management.

It is necessary to have a procedure in place for dealing with hypersensitivity reactions and the equipment necessary for resuscitation before administering platinum compounds. Patients should also be advised of the possibility of adverse reactions, and that they should notify medical personnel as soon as possible if they notice them [28].

Management in case of allergic reaction

In case of allergic reaction, anti-allergic medications (steroids, antihistamines) should be given and a slower infusion of the cytostatic should be used (prolonged from 30 minutes to 3 hours). In this situation, it is sometimes possible to complete the entire scheduled dose of cytostatic agent, but it is important to remember that despite the use of additional drugs in premedication, there is still a high risk of sensitization. There

have been reports in the literature [13] that if a patient receives 8 carboplatin infusions without complications, premedication should be increased before the administering the next course in order to reduce the risk of an allergic reaction.

Management of allergic reactions to platinum compounds

If allergic reactions to carboplatin occur, one possible treatment modification is substitution with cisplatin. Cross-reactivity between cytostatic agents has not been proven, so in case of hypersensitivity to one of the platinum analogues, their replacement — carboplatin with cisplatin or cisplatin with carboplatin — should always be considered [11, 44].

A second possible scenario is to attempt to desensitize the patient (desensitization). A carboplatin desensitization procedure should be used if there is a high risk of anaphylaxis. Carboplatin administration in a desensitization procedure does not affect response according to RECIST criteria [45].

In the situation of planned desensitization to carboplatin, an appropriate procedure should be sought and then tailored to the circumstances of the given unit.

Contraindications to desensitization include [46]:
— patient fear and lack of consent;
— late sensitization reactions after carboplatin (more than 24 hours);
— erythema multiforme;
— Stevens-Johnson syndrome;

One option for premedication in a desensitization protocol is the administration of an oral steroid (dexamethasone) for several days prior to the protocol [21].

More than a dozen different carboplatin desensitization procedures have been described in the literature, with patient numbers ranging from 3 to 63. Different desensitization options, divided into 4 to 12 stages, were used in the presented procedures. Steroids, antihistamines, and H2 blockers were suggested for each procedure. Drug administration in desensitization was started from a few days before cytostatic administration to a few hours earlier and continued for a few days afterwards. The duration of cytostatic drug administration varied from 2 hours to 2 days [13].

It is important to note that desensitization procedures are time-consuming, but a greater treatment tolerance has been noted when cytostatic agents are administered at lower levels and for longer periods of time.

Making the decision to administer a cytostatic in a desensitization procedure always involves assessing the benefits and risks of the drug and informing the patient of all the consequences of the desensitization procedure, including the risk of anaphylaxis and even death. The patient should give informed written consent for foregoing the procedure.

Based on the literature presented at the Department of Gynecologic Oncology at the University Hospital of Lord's Transfiguration in Poznań, a desensitization protocol (Tab. 4) has been developed and is used in patients with grade 3 and 4 allergic reaction (according to the CTCAE v5.0) induced by carboplatin and cisplatin, for which platinum is an option according to the ESMO-ESGO 2019 guidelines [47].

Desensitization procedure — proceedings

The patient is hospitalized for approximately 3–4 days depending on the desensitization regimen being used. Before hospital admission, oral low-dose steroids (methylprednisolone at 4 mg, prednisone at 5 mg, dexamethasone at 4 mg once daily) are considered for several days, as well as antihistamines (clemastine, loratadine).

When a patient qualifies for chemotherapy, the desensitization procedure is preceded by obtaining informed written consent. On the day before carboplatin administration, intravenous steroids (in our case, dexamethasone at 8 mg) and antihistamines and H2 blockers are administered by oral or intravenous route.

When prescribing chemotherapy in a carboplatin desensitization protocol, the total dose of carboplatin is first calculated, usually 5–6 AUC. After calculating the total dose, the total is divided into four parts that will correspond to 4 bottles of carboplatin at increasing concentrations. Bottle 1 contains the cytostatic agent at a concentration of 0.1% of the calculated dose, bottle 2 contains 1%, bottle 3 contains 10%, and bottle 4 contains the remaining 88.9% of the calculated dose of carboplatin, respectively.

For example, with a calculated carboplatin dose of 700 mg, a prescription with the following doses is sent to the cytostatic laboratory:
— Bottle 1 — 0.7 mg carboplatin;
— Bottle 2 — 7 mg carboplatin;
— Bottle 3 — 70 mg carboplatin;
— Bottle 4 — 622.3 mg carboplatin.

On the day of scheduled chemotherapy, premedication begins in the morning and the following agents are administered:
— intravenous steroid;
— antihistamines such as loratadine, clemastine orally;
— and also H2 blockers in this case orally.

Administration of the first medication dose begins approximately 30 minutes after premedication.

Requirements for medical staff

1. The resuscitation team or ICU should be notified of a planned desensitization protocol with a high risk of anaphylaxis before a carboplatin infusion is

INDIVIDUAL MEDICAL ORDERS CARD

Name and surname ..... Age: ..... Department ……...

Medication: dose, dosage form and routes of administration																		
Enoxparin ..... — 1 × 1 *s.c.*				N				N										
Ranitydyna 1 amp *i.v.* lub famotydyna 1 pill po	M			8:00 pm	30 min before the carboplatin dose				9:00									
Cetirizine 10 mg po				8:00 pm					9:00									
Dexamethazone 8 mg; 20 mg *i.v.*				8:00 pm	8:00 am — 8 mg 30 min before the carbo. 20 mg				9:00									
Clemastine 1amp *i.v.*	M				30 min before the carboplatin dose													
Carboplatin 1 — 0.1% — 30–60 min. w 100–250 mL					►													
Carboplatin 2 — 1% — 30–60 min. w 100–250 mL					►													
Carboplatin 3 — 10% — 30–60 min. w 100–250 mL					►													
Carboplatin 4 — 88.9% — min. 1 h optymalnie do 3 h w 500 mL					►													
Ondasetron 8 mg w 100 mL 0.9% NaCl			►		►				►									
Sleep medications symptomatically							►		►									
Hydrocortisone 200 mg symptomatically					►													
500 mL 0.9% NaCl rinsing in case of allergy					►													
Phenazoline 1 amp im in case of allergy at the physician's discretion.					►													
Montelukast 10 mg Acetylsalicylic acid 150 mg	M M				M M				M M									
Prescribing physician's signature																		
Signature of the person performing the medical procedure																		

s.c. — subcutaneous; *i.v.* — intravenous; po (*per os*) — orally; M — morning; N — night

Table 4. Desensitization protocol used at the Department of Gynecological Oncology of University Hospital of Lord's Transfiguration in Poznań

Table 5. Effectiveness of using the desensitization procedure

Study	Patients/ovarian cancer n*	Number of protocols used n**	Procedures without any complications % (n)	Deaths during the procedure n
Lee et al. 2005 [45]	57/42	255	88.2 (225)	0
Castellas et al. 2008 [50]	98/ 65	413	67 (278)	0
Altweregr et al. 2017 [32]	129/109	788	96 (753)	1

*most patients were treated with platinum compounds; **depending on the number of stages (from 5 to 13) in a given protocol

started. The resuscitation team should be prepared to provide rapid assistance as needed.
2. One nurse should be assigned to the patient for whom the desensitization protocol is planned.
3. The physician should be present for the connection and initial infusion of chemotherapy; he/she should remain in constant contact with the nurse and patient, ready to respond immediately (known as direct single-person supervision).
4. Both the physician and the nurse should be trained to recognize early signs of an allergic reaction (e.g., the patient's involuntary scratching of the neck) to initiate anti-allergic treatment early enough.

The patient should be advised on the potential for hypersensitivity reactions each time before starting an infusion, during the desensitization procedure and the need to notify medical personnel immediately if alarming symptoms occur. This is important because 96% of the sensitization reactions observed during a desensitization protocol are skin symptoms [46]. For safety reasons and to ensure proper patient care during the desensitization protocol, it is not advisable to run two protocols at the same time on the unit.

The first three doses of the cytostatic should be dissolved in 100–250 mL of solution. The volume depends on the logistical ability of the nursing staff to administer the medication at the scheduled time. According to the experience from our unit, it is often not possible to set the pump to a volume of 100 mL, moreover it is difficult to transfuse 100 mL in 60 minutes. After several desensitization procedures, if there are no contraindications to more intravenous fluids, the first three concentrations are given in a volume of 250 mL over 30 min, max. 60 min. The rate of cytostatic agent administration is usually increased every 15 minutes at each of the carboplatin concentrations. The last of the concentrations (88.9% of the total dose) is dissolved in a volume of 500 mL with an administration time of 60–180 minutes, with a recommended increase in the rate of drug administration at 15 and 30 minutes of infusion. Premedication in the form of steroids, anti-allergic drugs, and H2 blockers is continued on the day the cytostatic infusion ends and on the following day.

There are reports in the literature of possible causes of some allergic reactions to carboplatin (redness, hot flushes). These may be related to vasodilation resulting from the sudden release of mediators such as prostaglandins and leukotrienes. To reduce the risk of mast cell activation, some centers recommend administering acetylsalicylic acid at 325 mg orally and montelukast at 10 mg orally once daily. These drugs are recommended from the next course in the desensitization protocol, when any sensitization reaction has occurred with the previous administration. Medications are given for 2 days earlier and on the day of cytostatic agent administration [48].

If a sensitization reaction occurs during administration of a cytostatic at the three lowest concentrations, administration of subsequent concentrations is not recommended, as it is associated with a high risk of a serious sensitization reaction. Likewise, if a grade 3 or 4 allergy (according to CTCAE v5.0) occurs at any level of desensitization.

In situations where grade 1 or 2 sensitization occurs during the administration of the last bottle of chemotherapy (highest concentration) and symptoms resolve rapidly after administration of anti-allergic medications, the administration of the remainder of the cytostatic agent may be considered, taking into account the benefits and risks of continuation, and guided by the patient's attitude and concerns.

In patients who develop symptoms of severe hypersensitivity to the drug, discontinuation is often necessary, and reintroduction of the drug is associated with a risk of developing anaphylactic shock and death [11]. The exact mechanism of action in desensitization is unknown, but it is thought that the process hyposensitizes mast cells and inhibits both their immediate and delayed activation [49].

Effectiveness of desensitization protocols

The effectiveness of desensitization protocols, e.g., for platinum compounds, has been evaluated in several studies as shown in Table 5. In all the cited studies, either no hypersensitivity reaction or less severe hypersensitivity reactions, compared to the original reaction, were observed when desensitization protocols were used.

Conclusions

Hypersensitivity to platinum compounds is a serious clinical problem, not only because of the possibility of causing anaphylactic shock and death of the patient. Platinum compounds are the primary medications used to treat some cancers, including ovarian cancer. If such a treatment is discontinued due to hypersensitivity, the patient's chances of survival are greatly diminished. The exclusion of platinum compounds from treatment also closes off the possibility of using PARP inhibitors in maintenance therapy that significantly extend disease-free time and overall survival.

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Disclosure of potential conflicts of interest

R. M has acted as a consultant and speaker for AstraZeneca and GSK and has served as a Board member for AstraZeneca, GSK is an investigator on PARPi trials with olaparib, niraparib.

A. Ch-G has acted as a consultant and speaker for AstraZeneca and GSK and has served as a Board member for AstraZeneca, is an investigator on PARPi trials with olaparib, niraparib.

J. S-R has acted as a speaker for AstraZeneca

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VIA MEDICA

REVIEW ARTICLE

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Precancerous lesions of the cervix — aetiology, classification, diagnosis, prevention

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ABSTRACT

The present review introduces the aetiology and classification of cervical precancers. The principles of diagnosis based on colposcopy are reviewed. The indications for colposcopy and targeted biopsy are steps in the diagnostic process of cervical precancers. Prophylaxis of these diseases prevents cervical cancer as high-grade precancerous lesions represent a direct precursor to cervical cancer. The basics of primary and secondary prevention, the types of screening, and the behaviour of the already-alerted patients after different screenings are presented.

Key words: colposcopy, targeted biopsy, cervical precancerous lesions, cytosmear, HPV vaccines, HPV screening

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Characteristics and classification of cervical precancers

Cervical cancer (CC) has precursors — cell changes can be detected by the so-called screening methods [1, 2].

These cellular changes are called dysplasia or CIN — cervical intraepithelial neoplasia (Europe), and SIL — squamous intraepithelial lesion (Bethesda, USA). They are classified as:

— mild dysplasia: CIN1/LGSIL (low-grade SIL);
— severe dysplasia: CIN2, CIN3 / HGSIL (high grade SIL) [1, 2].

Aetiology

Human papillomavirus (HPV) role in cervical carcinogenesis

HPV is one of the main aetiological agents for developing cervical precancers and cervical cancer (CC). Low-risk and high-risk HPV strains lead to low-grade dysplasia (CIN1/LGSIL1). Only high-risk HPV strains are responsible for disease progression [3].

There are over 100 different HPV subtypes. Only high-risk strains are responsible for cervical carcinogenesis (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66) and belong to class I carcinogens. HPV 16 and 18 are the two main subtypes associated with cervical cancer. The other important strains vary regionally. HPV 16 contributes to 50–55% of the cases of invasive cervical cancer. Collectively, HPV 16 and 18 are responsible for approx. 70% of cervical cancer. This infection is associated with certain risk factors [4, 5].

Risk factors for HPV infection:

— sexual behaviour (promiscuity, low sexual culture);
— smoking;
— eating habits;
— immunosuppression.

The so-called asymptomatic HPV carriers happen in 5–20% of sexually active women of reproductive age. HPV infection is very often reversible. About 90%

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of HPV infections can regress spontaneously within 24–36 months [3, 5].

The incidence of HPV infection is 7% for the age range 20–25 years and less than 2% for women over 30 years of age. Persistent infection with high-risk HPV strains (16, 18) progresses to HGSIL and cervical cancer. It has been established that HPV infection expresses 2 oncogenes (oncoproteins) — E6 and E7, which in turn inhibit tumour suppressor genes (p53, retinoblastoma rb), causing uncontrolled cell division. Specific indistinct co-factors act as triggers since not every persistent infection with high-risk papillomavirus strains leads to cancer. The transformational period is inconsistent in different patients [3–5].

Diagnosis of cervical precancers

Histological diagnosis of these lesions is performed in two ways:

1. Colposcopy and targeted biopsy (pinch biopsy under colposcopic control);
2. See-and-treat strategy: in case of inconsistency between cytology (cytologically-signalled patients) and negative/unsatisfactory colposcopic evaluation, LLETZ (large loop excision of the transformation zone) is required, i.e., loop excision providing histological material for diagnosis [6, 7].

Colposcopy plays a key role in the diagnosis and treatment of cervical precancers [8–13].

— Colposcopy allows for the identification, location and outlining of CIN lesions on the cervix, vagina and vulva [8].
— Colposcopy is mandatory for diagnosing and treatment of CIN. It manifests the most susceptive areas where a targeted pinch biopsy should be executed [9].

The main indications for colposcopy are [10]:

1. Abnormal cytology;
2. HPV screening-signalled patients;
3. Contact bleeding.

The goals of colposcopy are [12, 13]:

1. To identify the site of pinch biopsy that is mostly suspected for HGSIL.
2. To establish the condition of the transformation zone (TZ) and the squamous-cylindrical epithelium border. Assessment of (un)satisfactory colposcopy.
3. To exclude the presence of invasive cervical cancer.

Targeted biopsy should always be performed under colposcopic control. Indications for targeted pinch biopsy are:

— before performing ablation based on colposcopic CIN data [14];
— in case of inconsistency between cytology and colposcopic finding [15];
— for histological verification of atypical colposcopic finding (low-grade — Grade 1 and high-grade — Grade 2) (Fig. 1, 2) [14–17].

TZ condition

A satisfactory (adequate) colposcopic examination is one in which the squamous-cylindrical epithelium border and the borderlines of the atypical epithelium are clearly visible. Unsatisfactory (inadequate) colposcopy is the one with an unclear squamous-cylindrical epithelium border and/or an unclear distal border of an atypical lesion [8–13] (Fig. 3, 4).

Colposcopic signs for early invasion [10]

1. Size of the lesion: the larger the lesion, especially if it covers the vaginal fornix, the more suspicious of microinvasion it is.

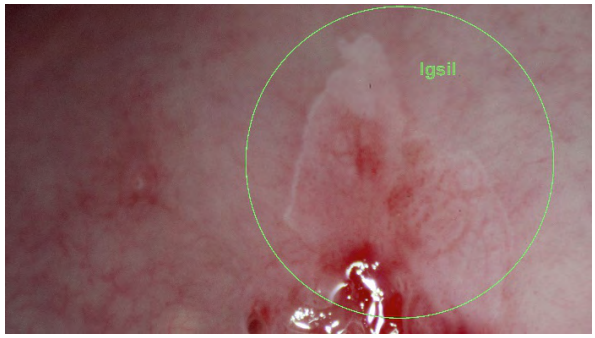

Figure 1. Low-grade Grade1 finding

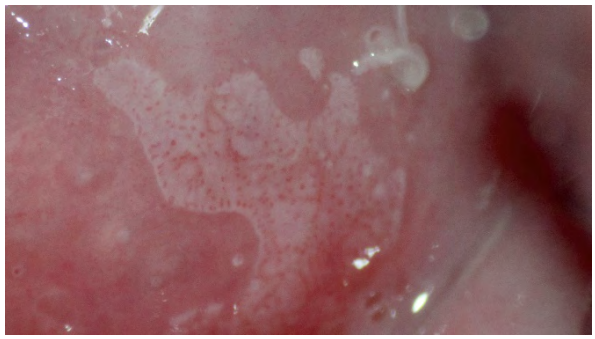

Figure 2. High-grade Grade2 finding

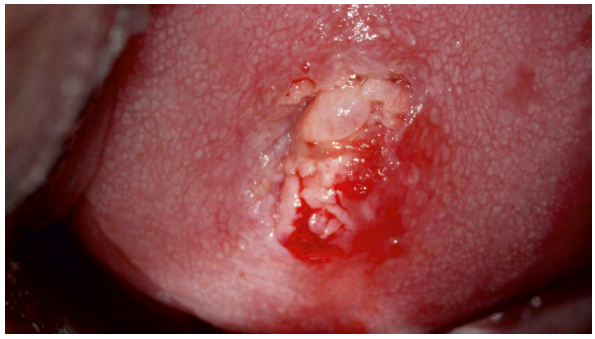

Figure 3. Low-grade atypia with visible borders of the lesion

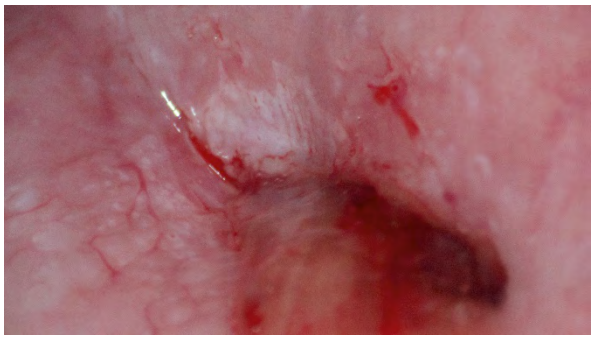

Figure 4. Unclear distal border of the atypical area

2. Different epithelial atypia in one lesion — "lesion in the lesion".
3. Increased vascularity.
4. Ulceration.
5. Raised edges — "mountain range".
6. Vascular atypia — different in calibre, direction, size.
7. Intense whitening ("chalk whitening") after acetic acid.

Prevention of cervical precancerous lesions (cervical cancer prophylaxis). Primary and secondary prevention

Primary prevention of cervical cancer

Cervical cancer has a clear etiological factor: HPV high-risk oncogenic strains. Exposure prevention to this factor is called primary prophylaxis achieved with vaccines against specific human papillomavirus strain. In Bulgaria, there are currently two vaccines available: Silgard — effective against strains 6, 11, 16, 18, and Cervarix — against strains 16, 18. By 2014, there have been 47 million vaccinated girls, according to WHO and the Global Advisory Committee on Vaccine Safety (GACVS). The safety of 175 million doses has been confirmed till 2013. As of 2014, GACVS has issued no comments on the vaccine's safety. No increased risk of autoimmune diseases, including multiple sclerosis, has been monitored as of 2015/16. More than 120 countries have approved HPV vaccines as part of their immunization calendars. The only recommendation is 15 minutes of follow-up after vaccination due to possible syncope after injection [18, 19].

Secondary prevention of cervical cancer

Detection of the so-called cervical cancer precursors — high-grade lesions CIN (2–3)/HGSIL and preventing their progression to invasive cancer through screening, behaviour signalling, follow-up, and possible treatment. Screening methods (screening programs) for secondary prevention have been developed [20, 21]. There are two types of cervical screening: organized (population-wide), which targets certain groups (by age and frequency/interval of studies), and opportunistic, which is not comprehensive and does not meet the criteria for a screening program. It is applied during a visit to a gynaecologist [20, 21].

Criteria for organized screening [20, 21]:

1. Mass screening: includes a specific target population during a specific screening interval.
2. Quality follow-up care and treatment of screening-positive women.
3. Effective communication between the individual components of the screening program (from screening to diagnosis and treatment).
4. High-quality screening tests, diagnostic assessment, treatment and follow-up care.
5. Adequate infrastructure, trained medical staff.
6. Financial resources.

Types of cervical screening

— HPV high-risk strains screening.
— Cytological — conventional and LBC (liquid-based cytology) [20].

HPV screening

It is characterized by high sensitivity: negative predictive value (NPV) — sensitivity to CIN3 > 95%, and low specificity — positive predictive value (PPV) [22]. The specificity (PPV) of HPV is lower than that of cytology (Cuzack 2006, Tab. 1).

Randomized trials have reached the following conclusions regarding HPV screening [22, 23]:

— HPV screening is a more productive and cost-effective method for reducing the incidence of cervical cancer.
— HPV screening allows for extended screening intervals but requires a high level of organization.
— HPV-positive patients undergo cytological screening.
— HPV screening is only suitable for women over 30 years of age.
— The integration of organized HPV screening and vaccination will make cervical cancer a rare disease.

The European guidelines for quality cervical cancer screening provide the following recommendations for primary HPV screening [22–24]:

Table 1. Sensitivity and specificity according to the cervical screening method

Method	Sensitivity [%]	Specificity [%]
Cytology	53.0	96.3
HPV typing	96.1	90.7

1. HPV screening (with oncogenic HPV tests) can be applied as organized (population) screening
2. The so-called Co-testing (HPV + cytology) should be avoided.
3. Only one primary screening method (HPV or cytology) should be used for the relevant age groups.
4. Routine primary HPV screening may begin over 35 years of age and not earlier than 30 years.
5. There is insufficient evidence of the applicability of this screening for the age group of 30–35 years.
6. HPV screening stops at 60–65 years, and the cytological screening provided that the last result is negative.
7. Cytological screening is used beyond the age range of primary HPV screening.
8. The screening interval after the HPV (–) test is between 5 and 10 years.

Behaviour and follow-up of HPV-alerted patients

There are three risk groups [25]:

A. Patients positive for HPV 16, 33 strains. The assessment is for very high risk; colposcopy is required, and readiness for treatment of CIN.
B. Patients positive for HPV 31, 18, 52, 35, 58 strains. The assessment is for high risk and requires colposcopy; HPV 18 causes endocervical lesions.
C. Patients positive for HPV 51, 68, 45, 39, 66, 56, 59 types.

The assessment is for intermediate-risk, and a new HPV test after one year is recommended.

In some countries, this type of screening is used for the first time [26]. In the United States, HPV positives for HPV16, 18 are referred for colposcopy. Positive for other high-risk HPV strains are subject to cytological examination. Colposcopy is recommended in cytologically-signalled patients. If the smear test is negative, new cytology is performed after one year. HPV-negative patients are subject to a new test in five years. In Belgium and the Netherlands, HPV negatives are subject to a new test in five years. The positives are smeared: if it is smear-positive, patients are referred for colposcopy; if the cytology finding is normal, the test is repeated after one year. If it is still normal, the woman is subject to HPV screening after five years [26]. Similar to the above is the screening system in Italy, where instead of repeated cytology, an HPV test is performed.

HPV screening challenges

The HPV test is characterized by high sensitivity (NPV) but low specificity. Increasing specificity can be achieved by testing for HPV types (16, 18, 33) and improving cytology by dual-stain cytology testing for p16 and Ki 67 — this study is a predictor of CIN 2–3. Testing for oncoproteins E6, E7 also complements the screening and manifests that persistent viral infection leads to changes in the cellular regulatory cycle [27, 28].

The combination of vaccination and HPV screening is fundamental to cervical cancer eradication programs [29, 30].

HPV vaccination programs include girls aged 12 to 14 years and provide 100% effectiveness against vaccine strains (if vaccinated before infection). In some countries, boys are also vaccinated [29].

Post-vaccination screening provides for an extended screening interval. In the future, patients will be able to take a screening sample themselves, the so-called self-sampling [29, 30]

Cervical cytology classifications

Cytological screening systems

There are three cytological screening systems used in practice [31]:

1. Papanicolaou system or PAP smear test.
2. The Bethesda system (TBS) — 2001, 2014.
3. The British Society for Clinical Cytology (BSCC) classification: used in the UK. According to this system, cellular changes are defined as:
   — borderline nuclear changes — BNC (HPV atypia — koilocytosis);
   — mild changes — corresponds to CIN1;
   — moderate changes — corresponds to CIN2;
   — severe changes — corresponds to CIN3.

The Bethesda system grades cellular changes as follows (2014):

1. Non-neoplastic cells.
2. Epithelial cells abnormality — these are cytologically-signalled patients. The changes can affect squamous cells and are described as atypical squamous cells of undetermined significance (ASCUS); atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H); LGSIL, HGSIL; and glandular cells.

Abnormal Cytosmear Recommendations

Abnormal Cytosmear Recommendations of the American Society for Colposcopy and Cervical Pathology (ASCCP) [32]:

In cases of ASCUS (atypical squamous cells of undetermined significance) or BNA (borderline nuclear abnormality), three lines of behaviour are recommended:

1. Repeat the smear after six months
   — if negative, repeat after six months;
   — in case of two negative results, return to routine observation;
   — if positive (ASCUS, borderline), the patient is referred for colposcopy.

2. Immediate colposcopy
   — in the case of normal colposcopy results — cytology after one year.
3. HPV (DNA) triage:
   — HPV positive results — colposcopy;
   — HPV negative results — repeated cytology after one year.

In the case of ASC-H (atypical squamous cells — can not exclude high-grade squamous intraepithelial lesion), the patient is referred for colposcopy:

— if the colposcopy result is negative — a new smear test is recommended;
— if the colposcopy and the new cytology are negative cytology after six months is recommended.

In the case of LGSIL/CIN1 (mild dyskaryosis), colposcopy is recommended.

— If the colposcopy result is normal — a new cytology test and/or HPV test is recommended.
— In the case of HGSIL result, the patient is referred for colposcopy and biopsy.
— If the colposcopy is satisfactory and the biopsy does not detect HGSIL, revision of cytology and histology is recommended. If HGSIL is detected — treatment with LLETZ is recommended.
— If the colposcopy is unsatisfactory, it is recommended to perform LLETZ (see-and-treat protocol).

Summary

Concerning terminology, CIN1 is classified as a low-grade squamous intraepithelial lesion (LGSIL) and CIN2/3 as a high-grade squamous intraepithelial lesion (HGSIL). High-risk HPVs (16, 18, 33) are responsible for the progression of the carcinogenesis process. Primary prophylaxis (vaccination) is highly effective. Secondary prophylaxis is based on the application of screening systems (HPV high-risk strains and cytology). In screening-positive women, colposcopy is most often performed with or without a biopsy. The diagnosis of precancerous lesions is histological after colposcopic evaluation (targeted biopsy or see-and-treat protocol).

Conflict of interest

The authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Assessment of the quality of life of patients with breast and cervical cancer

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ABSTRACT

The location of the tumor and the type of selected treatment are factors that determine the quality of life of patients. The incidence of neoplasms increases every year, with more and more patients successfully undergoing treatment processes but also struggling with the immediate and delayed effects of the disease and the treatment applied. A diagnosis of cancer is a critical situation in everyone's life, which may disturb their sense of agency, stability, and safety. Cancer significantly affects the lives of both patients and their families, and a diagnosis confirming cancer may disturb the sense of control over one's own health. According to numerous studies on the quality of life, depending on the location of the neoplasm, the reaction of patients to the course of treatment may have various psychological effects that will have an impact on the process of adaptation to the disease and psychosocial functioning.

Neoplastic disease, depending on its location, may affect the assessment of one's own body and function in the sexual sphere. The location of the tumor not only causes changes in patients' bodies and health options related to their physicality but also affects their coping strategies, self-perception, sense of influence on one's own health, and the quality of social relations.

The objective of this article is to assess the differences in the health-related quality of life among women suffering from breast and cervical cancers.

Key words: breast cancer, cervical cancer, quality of life, sense of control

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Introduction

Breast cancer is the most common neoplasm in women in Poland, and the second, after lung cancer, cause of cancer-related death, accounting for 22.5% of all cases among cancer patients [1]. The highest number of cases of breast cancer is reported in women over 50 [2–6]. According to the National Cancer Registry, the number of cases of breast cancer in recent years exceeded 16500 and is constantly growing. On the other hand, cervical cancer is the seventh most diagnosed cancer among women, accounting for 2.8% of all cases of cancer [1]. The most frequently diagnosed histologic subtype of cervical cancer is squamous cell carcinoma, which accounts for as much as 95% of all cases of cervical cancer [7, 8]. The development of oncological treatment methods is conducive to the increase in cancer survival and cure rates, while at the same time, researchers are paying more and more attention to the impact that the patient's psychological condition exerts on the treatment process and their quality of life following the treatment [3].

Cancer has consequences not only of a medical nature but also psychological and social. The diagnosis of the disease and the implementation of treatment significantly influences the current functioning of pa-

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tients and their social role, which changes from that of a healthy person to a sick person, and adds to everyday life the duties and procedures related to diagnostics and treatment. Psycho-oncological literature still devotes a lot of attention to the phenomenon of carcinophobia [9]. People diagnosed with this disease may experience a feeling of stigma and otherness, which may further lead to their isolation from relatives and society [9, 10]. Many studies emphasize the importance of social support during illness. A lack of acceptance and empathy, in particular on the part of relatives, may weaken the patient's motivation for further treatment, leading to withdrawal from treatment due to a feeling of loneliness, exclusion, and helplessness about the disease [11].

Disease symptoms and the selected treatment regimen are closely related to how patients function socially and the somatic symptoms they experience [12]. Researchers will focus more and more on the psychological functioning of the patients, emphasizing that it affects not only the effectiveness of therapy but also the quality of their life [13]. Knowing the differences in the functioning of patients and the importance of tumor location for their self-esteem and wellbeing will improve the work of medical staff caring for patients.

The concept of quality of life

Health-related quality of life is defined as: "the functional effect of the disease and its management perceived (experienced) by the patient" [14]. The World Health Organization (WHO) proposes to expand this definition by adding that: "health is the fullness of the physical, mental and social wellbeing of a person, not only the absence of disease or disability" [15]. This means that the way the disease is perceived is not the sole determinant of the patients' quality of life, and there are also other factors involved in the subjective assessment of the patient's wellbeing. Moreover, the absence of disease is not the only condition for satisfactory human wellbeing. A similar opinion was expressed by De Walden Gałuszko, who describes health as: "an assessment of one's own life situation made during the period of illness and treatment, taking into account their special role." Within this definition, four areas of health are distinguished: physical state, mental state, as well as somatic sensations, and social situation [16]. The state of health is undoubtedly included in the quality of life, and at the same time, this concept refers to the assessment of the life satisfaction of the respective person. Therefore, more and more attention in human functioning is focused on the social, psychological, and economic spheres because what we ultimately define as wellbeing requires subjective satisfaction with various spheres of human functioning [17].

The genesis of interest in the quality of life dates back to the 1970s, when medicine, due to the progress in the treatment of patients, began to pay attention to health and non-health consequences of chronic diseases. This is due to the emergence of a new approach in medicine that assesses the results of treatment not only on the basis of the duration of the patients' survival but also their subjective assessment of their life satisfaction [17]. In an attempt to define patients' quality of life, research took two basic directions: psychometric and qualitative. The first relates to the use of standardized psychometric scales to measure patients' ability to "perform basic everyday activities, the level of their mental (emotional) functioning, and social adaptation" [17]. The second line of research focuses on individual experiences and a subjective assessment of health and functioning during the disease [18]. The same authors distinguish the assessment of the quality of life in the effect of treatment, noting that it is important not only to assess the doctor but also the patient. The way the disease is comprehended, the selected treatment regime, as well as the duration of the disease, all affect the final assessment of patients' wellbeing. The researchers point out that the patient's perspective, including the evaluation of the quality of life and what is important for the patient at this particular moment are of particular importance in assessing the quality of life [19].

Patients' quality of life suddenly changes upon being diagnosed with cancer. Their current lifestyle and habits are disturbed, as patients have to adapt to the recommendations related to treatment and, importantly, a shift in their social role from that of a healthy person to that of a sick person. A diagnosis of cancer arouses anxiety and concerns about further health, and the treatment process and the associated undesirable effects lead to a reduction in the functioning and wellbeing of patients.

The quality of life of breast cancer patients — the effect of treatment

The quality of life of breast cancer patients depends on numerous factors. What is of particular importance, apart from the selected treatment, are patients' reactions to the diagnosis, the disease acceptance rate, and the adopted strategies of coping with stress [20]. The diagnosis of breast cancer involves changing one's entire lifestyle. As a result of a breast cancer diagnosis, women often feel fear, regret, anger, despair, and anxiety. These emotions are related to concerns about their future, including the treatment process, potential survival, and social functioning [18]. According to the researchers, what is frequently reported by patients as consequences of breast cancer and its treatment are fatigue, symptoms of gastric upset, nausea, vomiting, pain in the arm and shoulder, arm swelling, and difficulty breathing [21, 22].

Chemotherapy

Chemotherapy is one of the most common treatment regimens for breast cancer patients. This treatment reduces the quality of life not only through side effects such as nausea, chronic fatigue, abdominal pain, and weakness but also causes psychological deterioration in patients [3]. Women awaiting chemotherapy often experience fear of the treatment and their prognosis, but also of the change of their social role from that of a healthy person to that of a sick person, as well as physical changes related to the selected treatment (eg. hair loss) [23]. According to researchers, the psychological condition of patients is reduced due to emerging emotions such as fear, sadness, anxiety, and concerns about their appearance [2, 24]. Despite these fears and side effects related to chemotherapy, emotional support from their partner and family helps patients cope with the effects of the disease and emotions accompanying the treatment process [3, 17].

Hormone therapy

Hormone therapy is another method applied in breast cancer treatment. Hormone treatment causes inhibition of estrogen's influence on cancer cells (e.g. tamoxifen), which affects the homeostasis of the whole body and patients' quality of life. One of the most common side effects of this type of treatment are vasomotor symptoms, which include, among others: hot flushes, night sweats, and sleep disorders [25]. The use of hormone treatment in breast cancer affects the emotional condition of the patient, which can lead to low mood, a feeling of anxiety, or depressive disorders. Apart from their emotional situation, patients undergoing hormone therapy also complain of a deterioration of their sexual function and problems with chronic fatigue [25]. Mourits, Bockermann, de Vries et al. have a similar opinion on the effects of hormone treatment on the quality of life in patients subjected to it. According to these researchers, treatment with hormone therapy negatively affected the libido of patients, which resulted from secondary symptoms of the treatment in the form of dyspareunia or vaginal dryness [26–28]. In the same review, Jagielska et al. pointed out that hormone treatment is also associated with the risk of developing cancer of the endometrium, which may additionally trigger patients' anxiety during the treatment [25].

Surgery

Breast cancer often requires surgical intervention. Depending on the selected treatment strategy and the needs resulting from the development of the neoplastic lesion, the case conference may decide to perform a mastectomy. Currently, medicine ever more often opts for breast-conserving surgery or mastectomy with simultaneous breast reconstruction or reconstruction performed after the procedure.

The breast removal procedure has an impact on patients' quality of life. Mastectomy affects not only the physicality of the body but also functioning in everyday life and the patient's psychological condition. Hospitalization and the mastectomy procedure are a traumatic experience that disrupts all levels of psychological functioning.

According to Słowik, Jabłoński, Michałowska-Kaczmarczyk et al., a mastectomy "may be the underlying cause of numerous anatomical and physiological disorders. These include limb lymphoedema, decreased muscle strength, limited mobility of the hand in the joints, and postural defects" [2]. The same authors point out that the symptoms resulting from the applied surgical treatment affect the functioning of a woman in her everyday life, which translates into the overall quality of life and wellbeing of the patient. Pytka and Spych, who researched the impact of radical mastectomies on patients' quality of life, had a similar opinion on this subject [5]. According to these researchers, breast cancer and the selected treatment significantly reduce the quality of life in all spheres: psychological, social, professional, and intimate [5].

In the era of substantial development of oncological surgery and research on the quality of life, more and more attention is paid to the aspect of cancer patients' perception of their bodies. According to researchers, the very nature of the surgery and postoperative scarring affects not only the physical but also the social and psychological functioning of patients. This is because breasts belong to the area of female identification and, apart from their child-feeding function, they also have an aesthetic, sexual, and symbolic dimension that affects the patients, their self-esteem, and their perception of themselves as women. Based on many psychological observations, researchers identified the "half-woman complex" in patients after mastectomy without breast reconstruction. Symptoms attributed to this area of psychological functioning are decreased self-esteem, lack of acceptance of one's body, and decreased quality of intimate life. These symptoms result from the mastectomy procedure, which influences the perception of the aesthetics and attractiveness of one's body and the symbolism of femininity [2, 24, 29, 30].

Attitude towards the performed procedure also has a significant impact on wellbeing. The negative evaluation of the postoperative scar in the case of mastectomy was associated with a lack of appetite, depression, and irritability [2]. The same study noted that the assess-

ment of postoperative scar may vary depending on the economic situation of the patients and the support they received from their partners, family, and self-help groups. This proves that patients' socio-economic situation may be a psychological resource for coping with the effects of the disease [30].

Interestingly, Zegarski, Głowacka, and Ostrowska drew attention to the interdependence of the patients' financial situation after losing a breast on their assessment of the appearance of the postoperative scar. The worse the perception of the patients' financial situation, the worse their postoperative scar (mastectomy) was, which translated to a reduced assessment of their perceived quality of life [29]. Researchers assume that the above dependence may result from the perception of the positively assessed financial situation of the patient as an additional psychological resource of the quality of life, which could translate into better coping with the disease and treatment effects [29]. According to a number of studies, only 24% of patients remain professionally active during treatment. It is important, as both professional activity and acquiring funds for further treatment may modulate the overall functioning of the patient [29]. In the same publication, Zegarski et al. presented a conclusion based on many studies, which shows that due to the development of breast cancer and the treatment process, 78–88% of women experienced a reduction in their quality of life in the sexual sphere. Moreover, in studies on the quality of life, it was observed that the quality of sexual functions, sexual activity, and body-image perception were worse in the case of multimodal treatment than in the case of surgery alone. A particularly noticeable decrease in sexual function (eg. sexual drive) and self-esteem was noticed in the case of younger patients [29].

Stadnicka, Pawłowska-Muc, Bańkowska, and Sadowska, while examining the impact of emotional support from their partners on the quality of life of cancer patients after breast amputation, obtained results indicating that it had a significant impact on coping with the disease and the breast loss. The support of medical staff and support groups, such as Amazons or the Cancer Fighting League [29] also played an important role in the psychological and social functioning of the patients. Interestingly, the same researchers provide information that the partner's support has a positive effect on further functioning in the intimate sphere, which promotes the recovery of patients after mastectomy [29].

According to Naz, Darooneh, Salmani, et al., positive changes in patient attitudes towards the disease occur take place as a result of growing awareness about the treatment and are also related to education. Health beliefs are also closely related to the sense of agency, which is conducive to good health practices (e.g. following doctors' orders in connection with the treatment). In the same study, Naz et al. were able to confirm that higher education leads to greater access to health information, which influences the sense of health control [31].

Religioni, Czerw, and Deptała investigated the relationship between the location of the neoplasm and the psychological adaptation of patients to the disease. Among patients with breast, lung, intestine, and prostate cancers, breast cancer patients scored the highest in terms of showing "a fighting spirit," which meant that the affected women had a task-oriented approach to following doctors' orders and being involved in the treatment process. This result motivates us to further research the impact of cancer location on the quality of life and coping strategies [12].

Quality of life after breast-conserving surgery or breast reconstruction

Women who decide to undergo breast reconstruction, declare an improvement in their quality of life [32, 33]. Not having to wear a prosthesis is linked with psychological comfort, the freedom of image change, and a lack of stress related to the correct positioning of the prosthesis. This fundamental difference makes patients feel better in social contacts and have a significantly greater acceptance of their body image compared to patients who did not undergo reconstruction [34, 35]. The above factor is undoubtedly related to the symbolic meaning of breasts, which constitute an integral part of femininity.

The quality and type of breast reconstruction surgery are important in the assessment of women and their perception of their bodies. The studies by Edstrom-Elder, Brandberg, Bjorklund, et al. demonstrate that patients whose breasts were reconstructed using their own tissues assessed the procedure better than patients who received implants. According to the researchers, the procedure with the use of the patients' own tissues allowed to a greater extent obtaining breasts similar in size than the second method, which influenced the final assessment of patients and their quality of life [36].

What also affects the wellbeing of patients is the procedure waiting time. Women whose breast reconstruction surgery was performed immediately after mastectomy declared a better quality of life compared to women whose surgery was postponed [37–39]. This is because women who underwent simultaneous reconstruction did not have to deal with the discomfort associated with having a scar and concealing the effects of the procedure when compared to patients from the other group [17, 37, 38]. This proves the constant need to support and inform patients in order to prepare them for functioning after the surgery, both psychologically and socially.

Słowik, Jabłoński, Michałowska-Kaczmarczyk, et al. believe that the type of surgery performed has an impact on the subjective sense of the quality of life of patients [2]. There is a relationship between the type of surgery and the severity of pain symptoms in the breast. The conserving procedure was more likely (than the mastectomy) to trigger a greater intensity of symptoms (pain, swelling, and tenderness) in the examined women. In the case of mastectomy, a linear scar with a certain amount of subcutaneous tissue remains on the chest wall while in the case of a conserving procedure, a well-supplied and innervated part of the mammary gland remains, constituting a potential source of pain, swelling, and tenderness in this area. In the same study, it was noted that right-handed patients who had their right breast removed scored lower on the quality-of-life scales than patients with the dominant hand on the opposite side of their body. Removal of the breast on the side of the dominant hand is associated with a deterioration of functioning in the professional and intimate life [2].

In their research, Jankau, Trus-Urbańska, and Renkielska examined the impact of breast reconstruction surgery on the quality of life of patients after mastectomy. The researchers discovered that women with reconstructed breasts are more involved in family, social and professional life than patients who have not undergone breast reconstruction [17], who have to deal with the issue of masking an external prosthesis. Patients who decide to use a prosthesis often limit their social activity because they have a strong need to control the location of the prosthesis and mask the physical changes resulting from the removal of the breast [17]. Other authors demonstrate a similar opinion [37, 39]. According to the researchers, the earlier the age when a woman undergoes a mastectomy, the more difficult it may be for her to accept the changes resulting from the treatment process and breast loss [40]. Elderly women have a better perspective for the future, and they function better socially than younger patients undergoing mastectomy. The difference may be because young and middle-aged adult patients are at the stage when they have already met their social needs related to starting a family and having children while in the case of patients in later adulthood, these needs could have been satisfied many years before falling ill [41, 42].

The quality of life of cervical cancer patients — the effect of treatment

Cervical cancer most often affects women between the ages of 45 and 65. This means that this type of cancer affects a group of women who are most often still professionally and socially active; women who are wives and mothers. The diagnosis of cervical cancer diametrically disrupts their current functioning, influencing the performance of individual social roles, and thus, their wellbeing [43]. The diagnosis of cervical cancer often triggers anxiety in women, concerns about their further functioning, and a sense of a threat to their life. These types of sensations may persist even after treatment is completed. Patients may feel fear of relapse, anxiety, symptoms of depression, fear whether they will cope with tasks related to the implementation of social roles (as a mother and wife), and, importantly, they often declare reduced self-esteem and a sense of loss of attractiveness as women [43, 44].

The most common symptoms reported by women with this type of neoplastic disease include symptoms of premature menopause, insomnia, dyspareunia, vaginal dryness, vaginal shortening, hot flushes, constipation, complaints related to urination, sexual arousal, reaching orgasm, and achieving sexual satisfaction [21, 44–46].

Even though the effects of surgical treatment of cervical cancer may be invisible, in the sphere of social and professional functioning they have an impact on the perception of the patient's body and the quality of life [47]. Cervical cancer affects the current perception of one's body image, sense of femininity, and quality of sexual life. Numerous research reports suggest that patients' sexual experiences change both as the result of the treatment process and after treatment. Commonly reported symptoms include decreased sexual activity and interest in intercourse, decreased self-esteem, a sense of lost femininity and attractiveness [40, 48].

Bidzan, Rudnik, and Peplińska (2013) indicate two kinds of basic factors in the incidence of cervical cancer: the main and the contributing ones. The main factors include: "age, human papillomavirus infection, early onset of sexual life, a high number of sexual partners, high number of births, smoking, low socioeconomic status, previously identified pathology in pap smear, high-risk partners." The contributing factors include: "long-term use of hormonal contraceptives, improper diet, HIV infection, inflammation of genital organs caused by sexually transmitted pathogens other than HPV [9]. As with the case of breast cancer, chemotherapy, radiotherapy, surgery, and combination therapy are used to treat cervical cancer.

Depending on the case, the following methods are applied in the treatment of cervical cancer: "conserving surgery (conization, amputation), simple excision of the uterus with or without appendages, intravaginal and intrauterine brachytherapy, radical surgery with the selective removal of lymph nodes with or without adjuvant treatment, radiotherapy (teletherapy in combination with brachytherapy), radical hysterectomy with appendectomy and bilateral lymphadenectomy of the pelvic lymph nodes (the Wertheim-Meigs operation), primary radical surgical treatment with subsequent

radio-chemotherapy, radiotherapy combined with chemotherapy, and standalone chemotherapy" [9].

The quality of functioning during the development of cervical cancer is related to the patients' subjective sense of resourcefulness. According to Kozak (2002), patients with a strong sense of resourcefulness demonstrate better functioning in the emotional and cognitive spheres, which translated into their coping better with the hospitalization process resulting from oncological treatment [49].

According to Bidzan, Rudnik, and Peplińska, women with cervical cancer treated by surgery achieve high results of the quality-of-life assessment in the social, professional, and family spheres. An interesting exception in the presented study is in the sphere of sexual functioning where patients report poor quality of life [9].

Radio-chemotherapy

Kieszkowska-Grudny, Rucińska, Biedrzycka, and Nawrocki investigated the effect of combined treatment on the quality of life of patients suffering from cervical cancer. According to these researchers, after the disease and treatment, patients reported: lower back pain, fecal incontinence, hot flushes, sweating, and soreness of the vagina and vulva [43]. Like in the studies by Bidzan, Rudnik, and Peplińska, the authors drew attention to the sexual sphere of patients. The declared sexual activity of women with cervical cancer was reduced (with 38% of women sexually active in the last month after the completion of oncological treatment). Sexual disorders were associated with the symptoms of vaginal dryness, pain during intercourse, as well as low self-esteem, and other side effects related to the disease and the treatment process [9]. Dahiya, Acharya, Bachani, et al. reached similar conclusions when evaluating the impact of radiotherapy on patients' functioning [50]. These researchers add that both chemotherapy and radiotherapy are associated with sexual issues such as dyspareunia. Moreover, psychological factors also play an important role in sexual behavior. In the same studies, patients with cervical cancer experienced increased anxiety concerning their sexual performance [50].

Radiation therapy

Radiotherapy leads to anatomical and functional changes in patients' vaginas [16]. According to Donovan, Taliaferro, Alvarez, et al. the most frequent symptoms include menopausal symptoms, infertility, dyspareunia, vaginal dryness, short inelastic vagina, lack of vaginal lubrication, pain during sexual intercourse, and lack of sexual satisfaction [40, 44, 48].

Sang, Bae, Joo, et al. pointed out the characteristic effects of radiotherapy in cervical cancer. According to their research, women who survived cervical cancer reported: lymphoedema, diarrhea, constipation, financial difficulties, problems in social functioning, anxiety related to their sexual performance, and worse body image [46].

Discussion

The physical dimension of how women function during and after oncological treatment undoubtedly has a significant impact on their psychological condition and perception of their bodies, including their identity as women.

The abovementioned results of studies describing the psychological condition of women suffering from breast and cervical cancer suggest that the location of cancer and the psychosocial development stage of the patient (which in this case, means early or late adulthood) will affect the way patients perceive the disease is and deal with the stress. Depending on the age group and socioeconomic situation, patients will focus more or less on specific side effects of treatment and how hindering they are for the implementation of developmental tasks assigned to a specific age group (e.g. starting a family, sex life, having children) [41, 42].

Regardless of the location of cancer, it affects the woman's perception of her body image, sense of attractiveness, and femininity. According to research, the most important factor influencing the perception of one's own attractiveness is surgery, which leads to fundamental changes not only in the functioning but also in the appearance of the patient. Despite the differences, both groups of women reported a deterioration in their perception of themselves as women. The sole fundamental difference is the "half-woman complex" quoted in the research literature, diagnosed in women after mastectomy. The half-woman complex emphasizes the importance of physical values in the sense of female identity. The postoperative scar formed after mastectomy requires the women who are subjected to it to pay more attention to masking it with a prosthesis and to prevent this change from being noticed by others. The very fact of losing their breasts, despite the support of relatives, causes severe discomfort in women [2, 17, 24, 29].

Many studies prove that the support of loved ones, and especially of their partner, allows women to cope better with the effects of treatment. Support groups also play an important role in recovery and are of particular importance for patients' functioning in the psychological and social sphere. Therefore, there is a need for systematic work with patients and psychoeducation in dealing

with emotions and perception of the body image, and more broadly, of the woman's identity [51].

Conflict of interest

The authors have declared no conflicts of interest

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VIA MEDICA

REVIEW ARTICLE

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Causes of BIA-ALCL: a summary of the current state of knowledge

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ABSTRACT

The reasons for the development of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) have recently been quite a popular topic. The main interest is among plastic surgeons, surgical oncologists, hematologists, and oncologists. Over the past decade, numerous scientific papers on this subject have been published. Potential etiopathogenetic factors include the type of implants, biofilm, inflammation, microtrauma, and genetic mutations. None of the above potential causes have been adequately proven by scientific evidence; anyway, they should not be considered separately, as they are likely to coexist. Further research and exchange of experience among doctors and scientists are necessary to determine the leading etiopathogenetic factor. Its emergence would contribute to the rise of the possibility of using effective preventive measures in patients undergoing breast implant surgery and perhaps even eliminating BIA-ALCL.

Key words: BIA-ALCL etiological factors, breast implants, breast implant-associated anaplastic large cell lymphoma, complications of oncological and plastic surgery

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Introduction

BIA-ALCL, or anaplastic large cell lymphoma, is a rare cancer associated with breast implants. Although it develops within the tissue surrounding the implant, it is not classified as breast cancer [1]. This topic of BIA-ALCL has seen an increase in discussion in the medical community, primarily among oncological surgeons, plastic surgeons, hematologists, and oncologists. The first patient affected by this disease was reported in 1997 [2]. As of April 24, 2020, the American Society of Plastic Surgeons (ASPS) recognizes 903 cases worldwide. The data is based on a global network of international plastic surgery societies [3]. It should be assumed that this data is underestimated due to the lack of sufficient awareness of the problem in the medical world, as well as among patients, and the lack of reporting of each newly detected case to the appropriate, standardized registers. Several theories have been suggested in the etiology of BIA-ALCL — implant surface type, genetic factors, biofilm, inflammatory factors and implant microdamage [4].

Presumptive BIA-ALCL development theories

Implant surface

We distinguish implants with a smooth or textured surface, as well as — less often — covered with a titanium coating. Each of them has its pros and cons. The benefits of smooth surface implants are the feeling of having a natural breast, increased softness, ease of implantation, and the ability to perform a slightly smaller surgical incision. The disadvantages are greater mobility that can lead to the displacement of the prosthesis, which over time, can lead to stretching of its lower pole. In the case of implants with a textured surface, the benefits are higher resistance to friction and better implant stabili-

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ty, less risk of capsule contracture around the implant or rotation, and in the case of patients undergoing reconstruction using anatomical implants, the possibility of obtaining a natural upper pole, which reduces wrinkling (especially in prepectoral reconstructions). The relationship between textured surface implants and BIA-ALCL is relatively well established. Cases reported so far have only affected implants with such a surface. Twenty-four cases of incidence regarding patients with smooth surface implants reported to the FDA were not reliable or had a negligible medical history [3]. Collet et al. [5] point to the striking exponential increase in BIA-ALCL incidence in the last decade, which can largely be explained by the increasingly specific implant subtypes. Implants with a large surface and texture (class 4 surface) carry the highest risk of BIA-ALCL. The texture of Allergan implants is referred to as macrotexture. Its role was to reduce the risk of capsular contracture and minimize implant rotation. Countries that have provided confirmed statistics on BIA-ALCL cases, such as the United States, France, and Australia, reported that patients had just implanted macrotextured implants in most reported cases [6]. In July 2018, Egypt introduced a ban on the use of textured implants, while, as of November 21, 2018, the French National Agency for the Safety of Drugs and Medical Products (ANSM) recommends smooth implants. On December 19, 2018, CE certification was not renewed for Allergan Biocell and Microcell implants. On December 21, 2018, Brazil stopped selling Allergan Biocell. On February 7, 2019, Colombia suspended the sale of the same implants. Then, on February 2019, France conducted an ANSM hearing on the implants. On 25/26 March 2019, the hearing is conducted by the US Food and Drug Administration (FDA). In April 2019, France suspended the sale of macro-textured implants. On May 2, 2019, the FDA stated that Allergan does not meet the requirements for implants. In May 2019, Singapore and Canada prohibited the use of Allergan Biocell implants, and in November 2019, Australia prohibits the use of textured implants. On July 24, 2019, the FDA requested the voluntary withdrawal of Allergan Biocell implants and tissue expanders. Subsequently, the company withdrew from sales around the world. The FDA's request to Allergan was motivated by the increased risk of anaplastic large cell lymphoma associated with breast implants (BIA-ALCL). FDA investigation showed that the risk of BIA-ALCL associated with Allergan Biocell textured implants is about six times greater than the risk of BIA-ALCL associated with textured implants from other manufacturers. Further distribution of Allergan's textured Biocell implants would likely have serious adverse health consequences. Of the 573 reported BIA-ALCL cases worldwide, 481 patients had Allergan breast implants at the time of diagnosis. The Allergan Natrelle 133 and 133 Plus tissue expanders have not yet been associated with BIA-ALCL, yet they both have the same Biocell texture. Although tissue expanders are indicated for use for only six months, there is currently no information on how long of an exposure to Biocell texture can induce BIA-ALCL [7]. In turn, the type of surface used in Mentor textured implants is called Siltex. The coating of these implants has a rough surface that prevents the scar from growing around the implant. During the FDA Advisory Committee Meeting in March 2019 [8], it was stated that Mentor's Siltex texture is responsible for 1 case of BIA-ALCL out of 86,029 implants, while Allergan/Biocell for 1 case out of 3,345 implants, and Silimed's polyurethane implants 1 case our of 2,832 implants. The authors suggest that implants with a larger surface area, i.e., textured ones, give a higher chance of bacterial growth, which, when reaching a certain threshold, causes continuous immune activation, which leads to the development of lymphoma. After analyzing the above data, it can be presumed that the technology of implant production (Siltex vs. Biocell) may also play a role when it comes to the development of BIA-ALCL. The Brazilian company Silimed began the production of silicone breast implants covered with polyurethane foam in 1989. In 2008, the German company Polytech started producing its polyurethane implants, before selling implants in Europe under the name "Polytech Silimed" [9]. Both companies› implants are covered with the same foam. However, differences in production quality were identified [10], which may explain the differences in the incidence of BIA-ALCL — in Australia, 23 cases related to Silimed implants, and a case related to Polytech implants [11] .

Genetic factors

Genetic factors are thought to play an essential role in the pathogenesis of BIA-ALCL.

In a groundbreaking study by Blombery et al., mutations in the JAK-STAT3 pathway have been described for the first time [12]. The JAK-STAT3 pathway is the principal intracellular signaling pathway. Pathway abnormalities can be associated with a variety of disease entities — not just cancer [13]. It has been shown that improper activation of this path can trigger malignant transformation and contribute to the development of lymphomas [14]. Oishi et al. [15] in their work also showed that the JAK-STAT3 pathway is constitutively activated in BIA-ALCL, which in some cases is associated with recurrent JAK1 and/or STAT3 somatic mutations. These activating mutations, which may be parallel, were identified in 13% (3/23) and 26% (6/23) of BIA-ALCL, respectively. Other genetic changes include DNMT3A and TP53 point mutations. The ideal situation would be if every patient planned to undergo

implant surgery underwent genetic testing; however, due to the non-specificity of the above mutations, such action would not translate into its justification.

Biofilm

The biofilm may be a factor initiating the development of BIA-ALCL. The bacteria and the patient's tissue cells compete with each other on the surface of the implant from the moment it is inserted into the body. In 1987, Gristin described it as "race for the surface" [16]. The process of bacterial biofilm formation on the abiotic surface takes place in four phases: initial adhesion, permanent adhesion, maturation and dispersion [17, 18]. It is now believed that the pathomechanism of the development of peri-implant infection is complex and depends on the properties of the material forming the implant, bacterial virulence factors and the patient's condition [19, 20]. Among the features related to the surface of the material, the most important are the physicochemical properties and any unevenness formed during the material production stage (surface topography), favoring cell adhesion [21]. Textured breast implants carry a higher bacterial load than smooth implants [22]. The relationship between bacterial biofilm and T lymphocyte hyperplasia has been demonstrated in the pig and human model [23]. Chronic infection associated with breast biofilm is associated with T cell infiltration [22, 23]. After analyzing 26 breast implant samples in BIA-ALCL patients for biofilm and comparing them with 62 implant pouches in healthy patients, Hu H. et al. [24] found significant differences between the two groups. A higher percentage of Ralstonia spp. was detected in samples from patients with BIA-ALCL compared to patients without an implant. In contrast, the latter predominated over Staphylococcus spp. They considered that the detection of the microbiome in ALCL samples associated with the breast implant indicates a possible infectious cause. Because breast implants are widely used in both reconstructive and aesthetic surgery, strategies to reduce their contamination should be more widely studied and practiced. However, patients affected by BIA-ALCL do not appear to have a specific microbiome.

It is unclear how the microbiome might change for a patient with previous breast procedures and what role the surgery itself may play in manipulating the microenvironment [25]. Ralstonia spp. is also detected in patients without lymphoma [26]. Ralstonia spp. are nonfermenting Gram-negative bacilli found in soil and water. Ralstonia spp. have been reported in nosocomial infections resulting from contamination of medical solutions (e.g., water for injections, aqueous chlorhexidine solution) and are being increasingly recognized as a pathogen causing serious soft-tissue and implant-related infections [27–29].

Inflammatory theory

Chronic inflammatory processes are a known etiological factor in the development of cancer [30]. The relationship between some lymphoma subtypes and infectious agents has been demonstrated in many clinical studies and epidemiological observations. Due to the increasingly better access to advanced molecular techniques, the amount of detected infectious agents associated with the development of lymphomas may increase [31]. In turn, the presence of a foreign body such as a breast implant can cause local, chronic inflammation. Such suggestions are made in a paper published, among others, by Marshall et al. [32] in essence, it was found that the capsule around the implant presented features of chronic inflammation, including fibrosis, plasma cell hyperplasia, and lymphocytic infiltrates. Bizjak M. et al. [33] suggest in their work that patients with an inflammatory response to silicone implants should be closely monitored. They believe that implants — especially those used in the past — can cause chronic stimulation of the immune system against artificial material. As for implants covered with polyurethane foam, according to the paper by Handel N. [34], it stimulates the creation of a unique scar tissue that histologically differs from a tissue around smooth or textured implants. Non-polyurethane implants induce a relatively short-lived, sterile, and cell-free inflammatory response. According to the authors, polyurethane implants have a measurable advantage over smooth and mechanically textured gel-filled prosthesis. They do not seem to be associated with an increased risk of complications or morbidity. The authors also concluded that the capsular contracture after all types of breast surgery is significantly lower for polyurethane foam coated implants than for smooth or textured implants. This benefit persists for a long time, at least ten years after implant placement.

Implant microdamage

Brody, in his work, suggests that it is the textured surface of the implant that causes chronic trauma due to friction with the surrounding breast tissues, which can lead to neoplastic transformation [35]. Clemens M. also mentions recurrent capsule injury as a possible risk factor for BIA-ALCL, but these observations have not been confirmed in formal epidemiological studies [36]. In the work of Kaartinen I. et al. [37], we find a hypothesis about the development of BIA-ALCL as a result of repeated injuries caused by the interaction between the rough surface of the implant and the inner layer of its capsule. In general, relationships between injuries and tumorigenesis related to various organs have been shown in many works. Lauren A. Wise et al. [38] in a study conducted among African American women

found a positive relationship between being a victim of physical abuse in adulthood and the occurrence of breast cancer. The mechanism that would probably affect the occurrence of breast cancer in injured women is the chronic activation of the hypothalamic-pituitary-adrenal axis, which affects ovarian function and biosynthesis of steroid hormones involved in the etiology of breast cancer. In their pilot study, Rigby J. et al. [39] report that a causal relationship between physical trauma and breast cancer is likely. However, there is no reason to believe that trauma enhances mutagenesis. It is difficult to imagine how a single episode of injury can lead to a significant increase in cancer risk in the short term.

Injury can simply disrupt blood supply, release stimulating cytokines, or interfere with areas where ductal cancer exists in situ. This can accelerate the growth and timing of clinical signs of a tumor. Kuraishy A. et al. [40] report that many cancers develop in response to chronic tissue damage resulting in cell death, which increases the cancer potential of neighboring cells. Chronic tissue damage and inflammation have long been suspected of their ability to promote the development and progression of cancer, but only recently have these theories been supported by research on mouse models. Importantly, the experimental evidence obtained in mice is strongly supported by the analysis of clinical and epidemiological data in humans.

Discussion

Breast implant-associated anaplastic large target lymphoma (BIA-ALCL) has been described in the scientific literature for 20 years. In 2011, the FDA (US Food and Drug Administration) officially issued a warning that breast implants increase the risk of its occurrence [41]. The disease occurs in women after breast augmentation for aesthetic reasons and after repair surgery due to the pathology of the mammary gland. The change in surgical techniques and patient selection methods over years, as well patient monitoring strategies, may also be a reason for more widespread occurrence of this disease in certain time periods. So far, none of the theories have been officially recognized as the dominant etiological factors affecting the development of BIA-ALCL. However, it must be admitted that each of them has its logical justification and they are likely to coexist, ultimately leading to the development of BIA-ALCL. Genetic mutations can be the cause of BIA-ALCL as well as of any other affliction. They are an etiological factor mentioned in many diseases — as examined or presumed. On April 14, 2003, a report was published stating the completion of 99% sequencing of the human genome with 99.99% accuracy. However, the path to a thorough understanding of the gene mutations responsible for individual disease entities is still far away — the number of possible combinations is innumerable. In addition, it requires time and considerable financial outlays. In turn, biofilm or cutaneous physiological flora, as is commonly known in pathological conditions, ceases to be an ally of the human body. It can become a cause of infection of the surgical site and lead to the development of a chronic inflammatory process. Infection of the surgical site with skin physiological flora is a problem that increases the cost of therapy and harms the final result of surgical treatment. It is a very problematic issue for treatment teams. Despite the implementation of better and better prophylaxis methods, it is still one of the most common complications of surgical treatment. The incidence of surgical site infection is estimated to be in the range of 2–7% [42]. As for the surface of the implants, the analyzed literature draws attention to the clear percentage advantage of textured surface implants over smooth surface implants — it was recognized that those with a large surface and texture carry the most significant relationship with BIA-ALCL. The theory of the relationship between injury and tumor formation is the least described; however, reports on this topic have been published. Based on general medical knowledge, it can be suspected that the coincidence of the abovementioned factors further increase the risk of developing the disease, and also that some of them follow each other in a timely manner ultimately leading to the development of a tumor of the immune system with a starting point located in the breast implant pouch. Although the phenomenon of this disease is not a new problem, it still requires further research and dissemination of knowledge about it in the medical environment and sensitizing patients after operations using breast implants to the occurrence of symptoms such as swelling, nodules or fluid around the implant, asymmetry breasts, itching, pain or swollen armpit lymph nodes. Patients should be educated that when the abovementioned symptoms occure, they must immediately seek medical consultation. Similarly, before the surgery itself, one should inform about the existence of a disease entity, which is anaplastic large cell lymphoma associated with breast implants. In essence, the patient should be presented with the current state of knowledge, presumed causes, and information about possible treatment should be provided. The patient's consent to the operation must be informed. The growing popularity of the disease does not mean that every woman qualified for breast surgery using the implant is fully aware of the problem, and even more, as a layman, understands the essence of the disease and is aware of the complications arising from it. Meticulously discussion with the patient

might increase self-awareness and the motivation to report important symptoms. Operated women should know that self-examination is the important method of patient follow-up — probably even more valuable as first-line tool compared to imaging. At the same time, it should be emphasized that the risk of BIA-ALCL should not limit the use of this type of surgery, because this disease is relatively rare. In addition, urging doctors to report and detail BIA-ALCL cases in databases would undoubtedly contribute to a better understanding of the problem. Specialist cooperation in the discussed disease will allow the development of preventive and therapeutic strategies among diagnosed patients. There is a relative lack of prospective randomized studies comparing different types of implants. Probably BIA-ALCL is too rare to be detected this way, but the safety of the clinical approaches is best studied by long-term observation of prospectively collected cohorts, optimally with randomization. For example Peter G. Cordeiro et al. in their publication from 2020 claim that the incidence of BIA-ALCL (1:355 women) in their prospectively followed cohort is higher than previously reported in the literature, if it is about macro-textured breast implants. These results can be helpful for women undergoing breast reconstruction during the choice of implant type [43]. There are some ongoing researches basing on a similar model as for example: Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) Registry sponsored by The Lymphoma Academic Research Organization. The study is planned to last 13 years and should end in 2032 [44].

Conclusions

The causes of BIA-ALCL is certainly an interesting issue that requires further attention and research. There are several speculated etiological factors and it is currently impossible to say which of them plays a major role in the pathogenesis of the disease, but they should not be considered separately, as they are likely to coexist, ultimately leading to the development of BIA-ALCL. Activities aimed at better examination of this disease are highly recommended in order to undertake effective methods of preventing its development due to the widespread use of breast implants, especially in oncological surgery, where the possibility of reconstruction of the mammary gland reduces the trauma of women for whom the diagnosis of breast cancer itself is a dramatic event. Moreover emphasis should be placed on early detection of the disease by making patients aware of the possible occurrence of BIA-ALCL and convincing them to perform a thorough and regular breast self-examination which seems to be more valuable than imagine studies in early detection of the disease.

Conflict of interest

The authors report no conflicts of interest

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VIA MEDICA

REVIEW ARTICLE

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Maintenance avelumab in metastatic urothelial cancer patients

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ABSTRACT

The treatment outcomes of patients with metastatic urothelial carcinoma remain poor. Despite the relatively high response rate to platinum-based chemotherapy, the median overall survival doesn't exceed 14 months. Immunotherapy with anti-PD-1/anti-PD-L1 antibodies in the second-line treatment shows significant activity but nearly 50% of patients are not eligible for such treatment because of poor performance status. Therefore, there is a need for new treatment strategies. In the phase III JAVELIN Bladder 100 clinical trial, the maintenance treatment with avelumab in patients who achieved disease control with platinum-based first-line chemotherapy resulted in prolongation of overall survival and progression-free survival with good safety profile.

Key words: urothelial carcinoma, maintenance treatment, avelumab, immunotherapy

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Introduction

The prognosis of patients with metastatic urothelial carcinoma remains poor. The standard of first-line treatment is chemotherapy, preferable with cisplatin-based regimen due to the greatest therapeutic benefits [1]. Despite the objective response rate (ORR) of 50% and disease control in approximately 80% of patients, the median progression-free survival (PFS) is approximately 9 months, and the median overall survival (OS) is approximately 14 months [2]. Long-term disease control is achieved in approximately 10–15% of patients with metastases confined to lymph nodes [2]. In patients with contraindications to cisplatin, carboplatin-based regimens are used, but this treatment is associated with worse outcomes [3]. In patients who do not qualify to chemotherapy and have an expression of programmed death ligand-1 (PD-L1), it is also possible to use immune checkpoint inhibitors, such as atezolizumab (PD-L1 ≥ 5%) or pembrolizumab [in patients with a combined positive score (CPS) ≥ 10] [4, 5]. Immunotherapy has undoubtedly a well-established role in the second-line treatment after failure of platinum-based chemotherapy [2]. The European Medicines Agency (EMA) has registered pembrolizumab, atezolizumab and nivolumab in this indication [6–8].

Other second-line treatment strategies include rechallenge with platinum-based chemotherapy (if the first-line response was achieved and time to re-treatment is longer than 12 months), erdafitinib (in case of confirmed *FGFR2* or *FGFR3* gene rearrangement), or enfortumab vedotin (antibody–drug conjugate directed against nectin-4) [2].

It should be emphasized that only about 50–60% of patients who receive systemic treatment for metastatic urothelial carcinoma are eligible for second-line treatment, which is usually a consequence of the high dynamics of the disease and a significant deterioration of the general condition [9].

Therefore, it is necessary to search for new therapeutic strategies that can improve the prognosis of patients with metastatic urothelial carcinoma.

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Maintenance treatment

The concept of maintenance treatment is based on the continuation of therapy at a lower intensity after the disease control is achieved by earlier treatment [10]. It is aimed at delaying disease progression, worsening of clinical status, and prolonging OS. The drugs used in maintenance therapy should have good tolerability and a favourable safety profile. There are two strategies for maintenance therapy. The first strategy — continuation maintenance — is to continue the administration of one of the drugs used during induction therapy (an example is fluoropyrimidine monotherapy in patients with metastatic colorectal carcinoma who have responded to induction therapy with a multi-drug regimen) [11]. The second strategy — switch maintenance — is based on monotherapy with a drug not used in the current regimen [an example is the use of poly(ADP-ribose) polymerase (PARP) inhibitors] in patients with a serous ovarian, fallopian tube or peritoneal cancer with response to platinum-based chemotherapy [12–15].

Maintenance treatment in patients with metastatic urothelial carcinoma

Attempts have been made in the past to use maintenance treatment strategies in patients with metastatic urothelial carcinoma. The value of such approach was assessed in the phase II MAJA study (SOGUG 2011/02) [16]. A group of 88 patients who achieved disease control with platinum-gemcitabine chemotherapy with platinum and gemcitabine (4–6 cycles) were randomized to receive either vinflunine monotherapy (45 subjects) or best supportive care (BSC) (43 subjects). There was an increase in the median PFS [6.2 versus 4 months; hazard ratio (HR) = 0.59, 95% confidence interval (CI): 0.37–0.96]. However, this management was not approved due to the significant toxicity of vinflunine.

In another study, the efficacy of lapatinib (n = 116) was assessed versus placebo (n = 116) in patients with overexpression of human epidermal growth factor receptors-1–2 (HER-1–2), with disease control after 4–8 cycles of platinum-based chemotherapy [17]. There was no benefit from lapatinib therapy (median PFS 4.5 versus 5.1 months; HR = 1.07, 95% CI: 0.81–1.43; OS 12.6 versus 12 months; HR = 0.96, 95% CI: 0.70–1.31). Also, sunitinib was not active in maintenance therapy [18]. Median PFS was 2.9 months in the active treatment group (95% CI: 2.4–6.3) versus 2.7 months in the placebo group (95% CI: 2.5–7.2) (HR = 1, 0. 95% CI: 0.6–1.8).

On the other hand, the HCRN GU14-182 study assessed the efficacy of pembrolizumab in patients who achieved at least disease stabilization after platinum-based chemotherapy (1–8 cycles) [19]. Patients were randomized in a 1:1 ratio to pembrolizumab maintenance treatment or placebo. The median PFS was 5.4 months in the pembrolizumab arm versus 3.2 months in the placebo arm (HR = 0.64, p = 0.038). The study design allowed patients randomized to placebo to cross over to the active treatment arm after disease progression and finally, 52% recieved pembrolizumab.

Avelumab treatment for metastatic urothelial carcinoma

Avelumab is a human monoclonal IgG1 antibody directed against PD-L1 [20]. A feature that distinguishes avelumab from other anti-PD-1/PD-L1 antibodies is its potential to induce antibody-dependent cellular cytotoxicity (ADCC), which has been confirmed in preclinical studies [21], however, there is no data available indicating the clinical significance of this difference. Avelumab activity in the treatment of patients with locally advanced or metastatic urothelial carcinoma was confirmed in a cohort of patients with this diagnosis included in the phase I JAVELIN Solid Tumour study [22]. Treatment was associated with a good safety profile, the objective response rate with a follow-up period of at least 6 months was 17% (95% CI: 11–24), the median duration of response was not reached [22]. On this basis, the US Food and Drug Administration (FDA) approved avelumab, using the Accelerated Approval Pathway, for the treatment of patients with locally advanced or metastatic urothelial cancer who have progressed during or after platinum-based chemotherapy or within 12 months of completion neoadjuvant or adjuvant treatment.

The effectiveness of avelumab in maintenance treatment was assessed in the phase III JAVELIN Bladder 100 study [23]. The study included 700 patients who were randomized in a 1:1 ratio to treatment with avelumab or BSC. Treatment was initiated 4–10 weeks after chemotherapy completion. Patients received avelumab at a dose of 10 mg/kg every 14 days (the first 4 cycles with premedication with antihistamine and paracetamol). Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoints were OS in the general population and in patients with PD-L1 expression. Secondary endpoints were PFS, ORR, time to response, duration of response, disease control rate, and safety. The median OS in the general population was 21.4 months (95% CI: 18.9–26.1) in patients treated with avelumab versus 14.3 months (95% CI: 12.9–17.9) in the BSC group (HR 0.69, 95% CI: 0.56–0.86, p < 0.01). In patients with PD-L1 expression, the median OS was not reached in the avelumab group (20.3 — NR) and was 17.1 months (13.5–23.7) in the BSC group (HR 0,56; 95% CI, 0,40 — 0–79). The median PFS was in the general population in patients treated with avelumab 3.7 months (95% CI: 3.5–5.5) versus 2.0 months in the BSC group

(95% CI: 1, 9–2.7) (HR 0.62; 95% CI, 0.52–0.75), while in the group with PD-L1 expression — 5.7 months (95% CI, 3.7–7.4) and 2.1 months (95% CI, 1.9–3.5) (HR 0,56; 95% CI, 0.43–0.73), respectively. Next-line treatment was administered to 42.3% of patients in the group treated with avelumab and 61.7% of patients in the BSC group (43.7% received anti-PD1/anti-PD-L1 antibody). Immune-related adverse events (irAEs) were reported in 29.4% of patients receiving avelumab; in 7% of patients there were CTCAE (Common Terminology Criteria for Adverse Events) grade 3 events, but no grade 4 complications were found. Thyroid dysfunction was the most common irAE. The use of glucocorticosteroids at a dose of ≥ 40 mg of prednisone (or equivalent) was required in 9% of patients treated with avelumab.

In a subgroup analysis, the benefit of treatment with avelumab was found in all patients, regardless of PD-L1 expression, presence of visceral metastases, chemotherapy regimen (gemcitabine with cisplatin, gemcitabine with carboplatin) and the response obtained (stabilization, partial response, complete response).

During the 2021 Genitourinary Cancers Symposium (ASCO GU), an analysis of data from the JAVELIN Bladder 100 study was also presented, which assessed the benefit of avelumab treatment depending on the duration of first-line chemotherapy and the number of cycles administered (4–6). The benefit of maintenance treatment was found in all groups of patients [24].

US FDA and EMA approved avelumab for maintenance treatment of patients who have not progressed after platinum-based first-line chemotherapy.

Summary

The results of the JAVELIN Bladder 100 study are extremely important in the context of optimizing the strategy and sequence of treatment in patients with metastatic urothelial carcinoma. As mentioned, approximately 50% of patients who fail first-line treatment will not be eligible for further treatment. In this context, early use of maintenance immunotherapy after disease control by chemotherapy is warranted. From a biological point of view, the benefit of such a strategy may be related to the immunomodulatory effects of chemotherapy including depletion of T regulatory lymphocytes and myeloid-derived suppressor cells, as well as increased NK lymphocyte activity, neoantigens release and PD-L1 expression on tumour cells [25–29]. However, it should be taken into account that in approximately 10–15% of patients, long-term disease control can be achieved with chemotherapy alone [2], and in this group maintenance treatment will not be associated with any additional benefit. At present, however, no factors are allowing for the identification of these patients.

As part of the search for the optimal procedure, attempts have been made to combine chemotherapy with immunotherapy in first-line treatment. However, the results of KEYNOTE-361 [30] and IMvigor-130 [31] studies presented so far do not justify changing clinical practice (IMvigor-130 study showed benefit only for PFS with immature data for OS). The negative outcomes of clinical trials with chemoimmunotherapy in metastatic urothelial carcinoma may result — between others — from the fact that approximately 20% of patients in this population experience primary chemoresistance, that is associated with particularly poor prognosis and reduced benefit of immunotherapy.

Improving the treatment outcomes in patients with metastatic urothelial carcinoma is possible thanks to the introduction of new, active therapeutic strategies into clinical practice. The natural need is to determine the optimal treatment sequence and the possibility of combining them, e.g., with chemotherapy. The use of avelumab in the maintenance treatment of patients with metastatic urothelial carcinoma is a valuable therapeutic strategy, and the results of the JAVELIN Bladder 100 study provide the basis for defining a new standard of care in this group of patients, which was reflected in the recommendations of the European Society of Clinical Oncology (ESMO) [32], European Association of Urology (EAU) [33], and National Comprehensive Cancer Network (NCCN) [34].

Conflict of interest

Advisory and lecture fees from Merck and Pfizer. Travel grants from Pfizer.

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