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REVIEW ARTICLES

CASE REPORTS

CLINICAL VIGNETTE

VIA MEDICA

REVIEW ARTICLE

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Immunotherapy for colorectal cancer

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ABSTRACT

Progress in understanding complex interactions between cancer cells and the immune system has led to the development of new methods of treatment — immunotherapy, modulating the anti-cancer response of the immune system. For several years, colorectal cancer (CRC) was thought to be a cancer with low immune stimulation potential, but in recent years the favorable prognostic value of lymphocytic infiltrates in the tumor has been noted. Currently it is well known that the stimulation of the immune system by CRC cells is associated with the accumulation of mutations in DNA microsatellites. This phenomenon results from impairment of function of genes (mainly MLH1, MSH2, MSH6 and PMS2) encoding proteins involved in correction of mismatched nucleotides during replication (dMMR), whose phenotypic reflection is microsatellite instability (MSI). It affects about 15–20% of CRC, with clear differences depending on the stage of cancer — about 20% in stage II, 12% in stage III, and only around 4% in stage IV. dMMR/MSI cancers are highly immunogenic through overexpression of tumor antigens and can induce a deep immune response. Cancers with intact repair gene system (pMMR) and stable microsatellites (MSS) show poor immunogenicity, which makes it difficult to induce an anti-tumor immune response. The relationship between impairment of the mismatch repair system and the induction of an anti-cancer immune response justifies the use of checkpoint inhibitors of this response in the treatment of patients with CRC MSI/dMMR. In MSS/pMMR cancers, checkpoint inhibitors used in monotherapy are not effective. However, studies are underway to combine these drugs with other methods of systemic treatment (chemotherapy, EGFR inhibitors, angiogenesis inhibitors, MET inhibitors), as well as radiotherapy.

Key words: colorectal cancer, immunotherapy, microsatellite instability, MSI/dMMR, microsatellite stable colorectal cancers, MSS/pMMR

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world and the second leading cause of cancer-related deaths. There were 1.9 million new cases of CRC and over 900 000 deaths considered CRC-related in 2020 worldwide [1].

Overall mortality from CRC is slightly decreasing, but survival in advanced disease remains unsatisfactory. Median overall survival (OS) in patients with metastatic CRC does not exceed 3 years [2]. For this reason, new, more effective methods of treatment are constantly being sought.

For decades, chemotherapy based on 5-fluorouracil (5FU) has been the mainstay for CRC patients. At the end of the 20th century, irinotecan and oxaliplatin were introduced, allowing for doubling median OS [3]. Further improvement was achieved in the 2000s with the use of monoclonal antibodies inhibiting proliferation and angiogenesis. The first group includes

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cetuximab and panitumumab — antibodies directed against the epidermal growth factor receptor (EGFR), registered for the treatment of CRC patients without mutations in the *KRAS* and *NRAS* genes. Angiogenesis inhibitors include bevacizumab [an antibody that binds to the vascular endothelial growth factor receptor (VEGFR) ligand], aflibercept (a recombinant fusion protein consisting of fragments of the extracellular domains of VEGF receptors 1 and 2), and ramucirumab (an antibody directed against VEGFR) [4]. A slight prolongation of median OS can also be achieved by using regorafenib (a small molecule inhibitor of angiogenesis signaling pathway) or trifluridine/tipiracil (a combination of an anticancer thymidine nucleoside analog and a thymidine phosphorylase inhibitor) in subsequent lines [5, 6]. In recent years, a combined molecularly targeted treatment for CRC patients with the $BRAF^{V600E}$ mutation — cetuximab and encorafenib (a small molecule inhibiting BRAF kinase) has also been registered. Improved survival is probably also observed, to some extent, due to the introduction of a multi-specialist approach to the treatment of advanced disease, as well as improved supportive care.

Over the past decade or so, accumulation of knowledge about complex interactions between cancer cells and the immune system has led to the development of new methods of treatment — immunotherapy, which modulates the anticancer response of the immune system. Introduction of immune checkpoint inhibitors, such as monoclonal antibodies against cytotoxic T cell antigen 4 (CTLA-4 — ipilimumab, tremelimumab), programmed death receptor 1 (PD-1 — nivolumab, pembrolizumab, dostarlimab), and its ligand (PD-L1 — atezolizumab, durvalumab, avelumab) has significantly changed the treatment landscape for various cancers, including melanoma, lung, head and neck, kidney, bladder, and Merkel cell carcinoma. Immunotherapy has also been used in the treatment of CRC patients, but so far, its effectiveness has been confirmed only in the group of patients with deficient DNA mismatch repair (dMMR) and the phenotypic reflection of this disorder, e.g. microsatellite instability (MSI). In the remaining population of CRC patients, the value of such treatment has not been demonstrated [7].

The importance of the immune system in colorectal cancer

One of the most important factors modulating the tumor microenvironment, apart from somatic mutations and epigenetic regulation of gene expression, is the interaction of cancer cells with immune cells. The immune system is a set of innate and adaptive regulatory mechanisms that modulate immune activity by promoting tolerance to self-antigens and triggering reactions against foreign antigens, including cancer. As a tumor develops, the ability of the host's immune system to recognize tumor antigens and destroy cancer cells gradually decreases. Cancer cells demonstrate many mechanisms to escape immune surveillance (e.g. secretion of cytokines promoting regulatory T cells and myeloid-derived suppressor cells to inhibit CD4+ and CD8+ cytotoxic T cells, loss of normal MHC class expression, making them invisible to T cells, and finally increasing expression of immune checkpoint proteins — PD-1 or PD-L1, which results in T cells exhaustion). In order to reverse these unfavorable mechanisms, various strategies are used to increase the ability of the immune system to recognize and destroy cancer cells [8, 9]. The above-mentioned immune checkpoint inhibitors are already widely used, and further strategies are still in various phases of clinical trials [10].

For several years, CRC was thought to be a low-level immune-interfering cancer. Recently, however, many studies have reported the favorable prognostic significance of tumor-infiltrating lymphocytes [11]. In addition, a large variation of the immune activity in different CRC molecular subtypes was observed. The CMS1 subtype (immunogenic, approx. 14% of cases) and CMS4 (mesenchymal, approx. 23% of cases) are immunologically active, "hot" tumors, usually with intense lymphocyte infiltration in the histopathology, while the CMS2 subtype (canonical, approx. 37% of cases) and CMS3 (metabolic, about 13% of cases) are "cold" tumors and lack an immunological activity [12]. Currently, the ability of CRC cells to interact with the immune system is associated with the accumulation of unrepaired mutations in DNA microsatellites.

Microsatellites are short stretches of DNA that consist of many repeats of one to ten nucleotide base pairs. During DNA synthesis by DNA polymerase, these sequences often undergo mutations, such as nucleotide insertions or deletions, leading to a shift in the reading frame of the genetic code. The system responsible for repairing such mismatches — MMR, which includes mutator genes, mainly MLH1, MSH2, MSH6, and PMS2 — plays a major role in recognizing and correcting errors in the microsatellite region, thus preventing genomic changes [13]. Mutations in the genes listed above result in accumulation of mismatches and instabilities in microsatellites. According to the European Society for Medical Oncology (ESMO) guidelines, MSI or dMMR testing is recommended in all CRC patients [14]. The polymerase chain reaction (PCR) test, e.g. the Bethesda panel, or next-generation sequencing (NGS) is used to determine microsatellite instability (MSI) or the IHC test to evaluate the expression of MMR proteins. Both methods are costly and require additional sections of tumor tissue in addition to routine

hematoxylin and eosin (H&E) staining [15]. Moreover, the guidelines treat MSI or dMMR determination equally. Due to the limitations of both these methods and the risk of false-positive results, the value of double determination — MSI and dMMR — is more and more often indicated [16]. There are also ongoing tests with use of artificial intelligence and machine learning to determine MSI/dMMR in routine histological preparations, which would be cheaper and faster than molecular diagnostics. However, the clinical use of this technology requires high efficiency and multi-center validation, which has not yet been achieved.

In the literature describing MSI/dMMR testing, there are various classifications of these disorders. Until recently, depending on the percentage of abnormal microsatellite regions detected in individual assays, a distinction was made between cancers with a high (MSI-high, MSI-H) or low degree of instability (MSI-low, MSI-L) or microsatellite stable (MSS) cancers. Clinically, dMMR corresponds to the MSI-H phenotype, while the MSI-L or MSS phenotypes correspond to MMR-proficient tumors. Recently, the following classification has become more common:

— cancers with microsatellite instability (MSI), corresponding to dMMR, also referred to as MSI/dMMR,
— cancers without microsatellite instability — MSS corresponding to pMMR, also referred to as MSS/pMMR.

This approach was introduced by the panel of experts from Bethesda and is also used in the ESMO guidelines [17, 18]. Such nomenclature has been adopted in the present work although when citing clinical trials, the original provisions used in the publications have been retained.

The presence of MSI, determined by a deficiency of one of the proteins of the MMR system, was found in about 15–20% of CRC patients, with distinct differences depending on cancer stage, i.e. approx. 20%, approx. 12%, and only about 4% in stages II, III, and IV, respectively [19]. These differences are explained by the overexpression of cancer antigens in tumors with such a highly mutated phenotype, which is supposed to result in increased immunogenicity of the tumor and induction of a deep host immune response, i.e. better control of the tumor by the immune system. Thus, MSI tumors are not only more frequently observed in the early stages, but also have a better overall prognosis [20]. MSS/pMMR CRC show poor immunogenicity, which makes it difficult to induce an anticancer immune response [21].

The majority of MSI/dMMR CRC are sporadic tumors associated with an epigenetic disorder — hypermethylation of the MLH1 gene promoter, which leads to its transcription silencing and lack of expression of the encoded protein. A higher incidence of sporadic microsatellite instability is associated with older age, female sex, right-sided location of the primary tumor, high grade of histology, mucinous, medullary, or signet ring cell histology, and the presence of lymphocytic infiltrates. Sporadic MSI-H colorectal cancers show a higher percentage of *BRAF*^{V600E} mutations (30–40%) compared to other cancers. The presence of the *BRAF*^{V600E} mutation is a criterion excluding germline disorders of mutator genes and is used as a molecular marker of sporadic MSI cancers [22].

About one-third of dMMR CRC is associated with the presence of germline mutations. In rectal cancer, MSI is less common than in colon cancers — about 5% of cases, but the majority of such cancers (84%) are caused by a germline disorder [23].

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC) is the most common genetic disorder associated with germline mutations of one of these four mutator genes. The most common mutation is in the *MLH1* or *MSH2* genes (42% and 33%, respectively), and less frequently in the *MSH6* and *PMS2* genes (18% and 7%, respectively). The syndrome is inherited as autosomal dominant and is associated with an increased predisposition to CRC (the risk is 30–73%) and endometrial cancer (30–51%), as well as ovarian, gastric, small intestine, and pancreatic cancer. A rare variant of Lynch syndrome that is associated with hereditary MSI is the germline exon 3 deletion in the *TACSTD1* gene encoding the EpCAM protein. This disorder leads to congenital epigenetic loss of *MSH2* gene function.

Other genetic syndromes associated with increased risk of CRC include:

— Muir-Torre syndrome, associated with a simultaneous germline mutation of the *MSH2* and *MLH1* genes and additionally characterized by the presence of seborrheic skin tumors;
— Turcot syndrome caused by a congenital mutation of the *APC* gene and one of the mutator genes *MLH1* or *PMS2* and associated with familial polyposis with the coexistence of primary brain tumors [24].

Immunotherapy for colorectal cancer

The relationships between disorders of the DNA *mismatch repair system* and the induction of an anticancer immune response justify the use of immune checkpoint inhibitors in the treatment of patients with MSI/dMMR CRC. Currently, there are two such inhibitors targeting the PD-1 receptor (pembrolizumab and nivolumab) and one directed against CTLA-4 (ipilimumab), which have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the last 5 years for patients with MSI-H/dMMR CRC.

The results of the phase-II study KEYNOTE-016 with pembrolizumab provided the first evidence of immunotherapy effectiveness in patients with metastatic MSI-H/dMMR CRC. The study involved 42 patients: 11 patients with dMMR CRC, 21 patients with pMMR CRC, and 9 patients with dMMR metastatic cancer other than CRC. All patients were heavily pretreated with all standard treatment methods. The objective response rate (ORR) in the group of patients with MSI-H/dMMR CRC was 40% [25]. In a later analysis, including 54 patients, presented at the 2016 American Society of Clinical Oncology (ASCO) Annual Meeting (not published yet), the ORR increased to 50%, and in patients with dMMR cancers other than CRC was even higher (71%). However, in the subgroup of patients with MSS/pMMR CRC, there were no objective responses (0%). Based on the results of this study, together with the results of four other phase Ib and II studies (KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158), the FDA approved pembrolizumab in 2017 for the treatment of patients with MSI-H/dMMR CRC after failure of conventional chemotherapy. Based on the results of additional cohort analyses from the aforementioned and other trials, this registration was then extended to all dMMR tumor subtypes in patients who had exhausted standard treatment options [26]. It was the first tissue agnostic drug approval of the neoplastic disease.

The aforementioned KEYNOTE-164 phase-II study evaluated the efficacy of pembrolizumab monotherapy after failure of 5-FU-based combination chemotherapy in a subgroup of 124 patients with MSI-H/dMMR CRC. The response rate was 34%, and after 3 years of follow-up, the response to treatment was maintained in 92% of patients [27].

In the randomized phase-III study KEYNOTE-177, pembrolizumab monotherapy was compared to the standard first-line treatment — doublet chemotherapy with the addition of a biological agent (bevacizumab or cetuximab) — in patients with MSI-H/dMMR CRC. The primary endpoints of this study were progression-free survival (PFS) and OS. The use of pembrolizumab was associated with a significant increase in median PFS (16.5 *vs.* 8.2 months), a reduction in the risk of progression (HR = 0.60; 95% CI 0.45–0.80; p = 0002), a higher ORR (44% *vs.* 33%), and prolonged median duration of response. After 2 years of follow-up, the response to treatment was maintained in 83% of patients treated with pembrolizumab compared to 35% treated with chemotherapy [28]. Median OS was not reached in the pembrolizumab group compared to 36.7 months for chemotherapy (HR = 0.74; 95% CI 0.53–1.03; p = 0.0359). This result was not statistically significant due to the assumed alpha level > 0.0246, resulting from the planned interim OS analyses and repeated testing [29]. Interpretation of the result was complicated by the fact that 60% of patients treated with chemotherapy received immunotherapy after progression. The rate of grade 3 and 4 adverse events for pembrolizumab was 22% *vs.* 66% for chemotherapy. A clinically significant improvement in the quality of life of patients receiving immunotherapy has also been demonstrated [30]. However, it should be noted that primary disease progression was more common in the immunotherapy group — 30% *versus* 12% in the chemotherapy group.

Based on these studies, EMA approved pembrolizumab monotherapy in patients with metastatic MSI-H/dMMR CRC in first-line treatment and after previous fluoropyrimidine-based combination therapy.

The efficacy of nivolumab in patients with metastatic MSI-H/dMMR CRC was confirmed in a phase-II multi-cohort study CheckMate-142, in which nivolumab was used as monotherapy or in combination with ipilimumab in the first or subsequent treatment lines. The first cohort included 74 previously treated patients who received nivolumab monotherapy (3 mg/kg every 2 weeks). The second cohort consisted of 119 treatment-experienced patients who received a combination of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) every 3 weeks for the first 4 cycles, followed by nivolumab (3 mg/kg) in monotherapy at two-week intervals. The third cohort consisted of 45 patients who received combination immunotherapy as first-line treatment. In patients treated with nivolumab alone, the ORR was 31%. After 12 months of follow-up, one-third of these patients were still progression-free [31]. The 5-year survival rate in this cohort was 46%. Combined immunotherapy resulted in an ORR of 65% in the second cohort, including 13% of complete remissions. Three-quarters of patients had received two or more prior treatment lines. The 5-year PFS and OS rates were 52% and 68%, respectively [32, 33]. Patients from the third cohort achieved similarly favorable results although the follow-up time in this cohort is much shorter. The compilation of these results may indicate that combined immunotherapy is more effective than nivolumab alone, but these two strategies have never been directly compared.

Based on the results of the CheckMate-142 study, EMA approved ipilimumab in combination with nivolumab for the treatment of patients with advanced dMMR/MSI-H CRC after prior fluoropyrimidine-based combination chemotherapy.

Immunotherapy for advanced MSS/PMMR colorectal cancer

More than 80% of advanced CRCs are MSS/pMMR tumors. They do not induce a significant immune response, and checkpoint inhibitors alone are not effective.

However, it is believed that the combination of these drugs with other methods of systemic treatment (chemotherapy, EGFR inhibitors, angiogenesis inhibitors, MET inhibitors) and radiotherapy may be a valuable option [34]. Studies evaluating the value of such combinations are ongoing, but so far, they have not been successful.

A promising strategy might be use of immunotherapy in combination with molecularly targeted treatment in patients with the presence of a molecular target, e.g. with the *BRAF*^{V600E} or *KRAS*^{G12C} mutation, and such studies are currently ongoing.

There is some hope for new-generation checkpoint inhibitors that could induce sensitivity to immunotherapy. An example of such a drug is botensilimab, an antibody directed against CTLA4 with a modified fragment crystallizable (FC) region to improve the activation of dendritic cells and NK cells. A phase-Ib study in which 41 patients with metastatic MSS CRC were treated with a combination of botensilimab and balstilimab (an anti-PD1 antibody) showed an ORR of 24%. An interesting observation was a lack of benefit from treatment in patients with liver metastases. This may indicate the important role of the tumor microenvironment in immunotherapy [35].

The future of immunotherapy in the treatment of patients with colorectal cancer

New indications

Apart from the above-mentioned directions of new research, which concern the combination of immunotherapy with other methods in patients with MSS CRC, there are studies assessing the value of immunotherapy in earlier treatment lines, including (neo)adjuvant treatment. Two studies on the use of immunotherapy in the first-line treatment of metastatic disease have already been mentioned (KEYNOTE 177 and ChechMate-142). The 3-arm COMMIT study compares atezolizumab monotherapy with FOLFOX chemotherapy combined with bevacizumab and FOLFOX chemotherapy combined with bevacizumab and atezolizumab in patients with advanced MSI/dMMR CRC. Data from preclinical studies show that chemotherapy containing oxaliplatin in combination with anti-angiogenic treatment increases the anticancer activity of the PD-L1 pathway [36]. Atezolizumab is also combined with standard chemotherapy (12 × FOLFOX) in the adjuvant treatment of patients with stage III MSI CRC. Such a combination aims to increase the activity of intratumoral cytotoxic CD8+ T cells (A021502NCTN) [37].

A small subgroup of patients with rectal cancer demonstrates MSI/dMMR. Early observations from a prospective study of 12 patients with locally advanced (94% of stage III) MSI/dMMR rectal cancer indicate high activity of immunotherapy. The study design was based on the administration of a PD-1 inhibitor, dostarlimab, 500 mg every 3 weeks for 6 months followed by radiochemotherapy (RChT) and surgery. Patients who achieved a complete clinical response defined by magnetic resonance imaging and endoscopic examination after dostarlimab could be actively monitored without RChT and surgery. The first 12 patients included in the study achieved complete clinical remission after 6 months of treatment with dostarlimab. They did not require any additional treatment and were actively monitored. By the time the results were published, the follow-up period ranged from 6 to 25 months. The treatment was well tolerated, and grade 3 and 4 side effects were not reported [38].

The multicenter non-randomized NICHE-2 study in patients with dMMR CRC assessed the effectiveness of neoadjuvant immunotherapy consisting of 1 dose of ipilimumab (1 mg/kg) and 2 doses of nivolumab (3 mg/kg) followed by surgery. The primary endpoint was safety and surgery feasibility after immunotherapy and the 3-year disease-free survival (DFS) rate. During the 2022 ESMO Congress, data on safety and pathomorphological responses to treatment were presented. The study evaluated 112 patients with a primary tumor stage of at least cT3, as assessed on the basis of a CT scan. cT4a or cT4b stage was found in 64% of patients, and N2 disease in 62% of patients. After initial immunotherapy, all patients underwent surgery. In the histopathological examination, 67% of patients achieved pathologic complete response (pCR) and 95% of patients had less than 10% of the residual tumor mass (MPR) [39].

The role of the microbiome

Another interesting area of research is the interaction of the gut microbiome with the immune system. Some studies indicated an association of changes in the gut microbiome with the risk of CRC as well as other cancers. Patients treated with immunotherapy achieve better results if their intestinal flora is not changed by antibiotic therapy [40, 41]. However, the actual impact of the gut microbiome in supporting immunotherapy is still not known.

Other methods of immunotherapy

Immunotherapy methods other than the aforementioned checkpoint inhibitors are also the subject of research. Many types of vaccines — autologous, peptide, and dendritic cell vaccines — have been studied in patients with CRC, but no survival benefits have been obtained compared to standard treatment

or placebo [42, 43]. The results of studies on the combination of vaccines with checkpoint inhibitors have so far been discouraging [44]. There is an ongoing study evaluating talimogene laherparepvec (T-VEC), which is a form of immunotherapy based on a derivative of the herpes simplex virus type 1, designed to replicate in tumor cells and produce granulocyte-macrophage colony-stimulating factor (GM-CSF). The idea is to enhance the immune response against cancer cells. In a study of patients with metastatic MSS CRC, T-VEC is injected into the tumor in combination with intravenous atezolizumab [45].

Therapy with T cells genetically engineered to express a synthetic chimeric antigen receptor (CAR) was very successful in the treatment of patients with refractory hematological malignancies, in particular B-cell acute lymphoblastic leukemia [46]. Different phases of studies are currently ongoing to extend CAR-T indications to solid tumors, including CRC [47].

Conflict of interest

B.R.: received remuneration from Merck, Amgen, BMS, MSD, GSK, Roche, and Servier, unrelated to the article.

M.G.: received remuneration from Merck, Amgen, BMS, MSD, and Servier, unrelated to the article.

M.K.: reports no conflict of interest.

T.K.: received honoraria from Roche, MSD, and BMS, unrelated to the article.

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VIA MEDICA

REVIEW ARTICLE

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Immunotherapy for gastroesophageal cancer

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ABSTRACT

Cancers of the esophagus, esophageal-gastric junction or stomach are one of the most frequently diagnosed cancers in Europe and in the world. They are characterized by a poor clinical prognosis, hence it is necessary to look for new, more effective methods of their treatment. The dynamic development of immunotherapy based on immune checkpoint inhibitors such as antibodies blocking receptor proteins CTLA-4, PD-1 or ligand for the programmed death receptor 1 (PD-L1) has led to a significant improvement in the effects of treatment of many cancers and initiated a number of studies evaluating the effectiveness and safety of immunotherapy in patients diagnosed with upper gastrointestinal cancer. The following paper presents the results of research that have become the basis for significant changes in the treatment strategy of patients with esophageal cell squamous carcinoma (ESCC), esophageal adenocarcinoma (EAC), adenocarcinoma of the esophagogastric junction (GEJ), gastric cancer, which are also reflected in the recommendations of oncological societies (NCCN, ASCO).

Key words: esophageal cell squamous carcinoma (ESCC), esophageal adenocarcinoma (EAC), adenocarcinoma of the esophagogastric junction (GEJ), gastric cancer, immunotherapy, PD-1, CTLA-4, CPS

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Epidemiology and etiology

Esophageal cancer

Esophageal cancer is the eighth most common cancer in the world and the sixth leading cause of cancer-related death [1]. It is diagnosed more commonly in *males* than females (2 to 8 times in different geographical zones) [2]. From a biological point of view, there are at least two different types of esophageal cancer. Esophageal squamous cell carcinoma (ESCC) is a neoplasm that in terms of molecular abnormalities is similar to squamous cell carcinomas of the head and neck region. Esophageal adenocarcinomas (EAC), as well as the *gastro-esophageal* junction (GEJ) cancer molecularly correspond to one of the 4 subtypes of gastric cancer, i.e. the chromosomal instability subtype. ESCC is the most common cancer worldwide although, in developed countries, the EAC rate is growing dynamically [3]. This is due to changing exposure to risk factors. For ESCC, they include low socio-economic status, consumption of tobacco, alcohol, hot drinks and nitrosamines, as well as deficiencies of vitamins C, E, and folic acid [4]. Risk factors for EAC include Barrett's esophagus, gastroesophageal reflux, obesity, and tobacco consumption [5]. Screening guidelines for the early detection of esophageal cancer have not yet been established, and there is a lack of scientific evidence to support their development. Esophageal cancer has a high mortality rate and poor prognosis. The 5-year survival rates do not exceed 20%, and median overall survival (OS) is about 9 months in ESCC

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patients and 11 months in EAC patients [6]. At diagnosis, distant metastases are found in about 40% of patients, and median OS in this group of patients does not exceed half a year. The results of clinical trials published in recent years have become the basis for a paradigm shift in the treatment of esophageal cancer.

Gastroesophageal junction cancer

In recent decades, the incidence of distal gastric cancer (GC) has decreased in Western countries, while the incidence of GEJ adenocarcinoma has clearly increased [7]. In the United States, the incidence of GEJ cancers has been increasing by 4–10% annually since the 1970s [8]. However, this growing trend should be interpreted with caution due to difficulties in obtaining consistent epidemiological data on the occurrence of GEJ cancer, which results from the heterogeneous definition of this cancer. For many years, GEJ cancers were classified as either esophageal or gastric cancers, or even "indeterminate" according to the World Health Organization's International Classification of Oncological Diseases. Despite this distinction in locations, there are still controversies in its definition, and cancers in this location are sometimes referred to as cancers of the lower esophagus or cardia.

In Asian countries, the definition of GEJ is based on the Nishi classification, according to which the GEJ region is defined as an area 2 cm above and below the Z-line. It includes not only adenocarcinoma but also squamous cell carcinoma. In Western countries, the Siewert classification has been widely used, according to which GEJ cancers are considered to be adenocarcinomas with the epicenter located 5 cm above or below the anatomical cardia [9]. The Siewert classification of GEJ adenocarcinomas includes:

— type I: 1–5 cm above the cardia, adenocarcinoma of the distal esophagus (almost the same as esophageal adenocarcinoma); it usually develops on the basis of intestinal metaplasia (Barrett's esophagus) and infiltrates the *gastroesophageal* junction;
— type II: carcinoma of the cardia, whose center is between 1 cm above and 2 cm below the cardia; develops on the basis of cardia epithelium or intestinal metaplasia;
— type III: 2–5 cm below the cardia; subcardial tumor infiltrating the *gastroesophageal* junction [10].

Barrett's esophageal adenocarcinoma is a cancer that typically corresponds to Siewert type II GEJ cancer.

According to the latest 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastases (TNM) classification, neoplasms infiltrating the *gastroesophageal* junction with the epicenter of the tumor located up to 2 cm below the anatomical cardia are staged and treated as esophageal cancers, while in the case of tumor epicenters located below 2 cm, as gastric cancers [11].

Factors that increase the risk of developing GEJ cancer include gastroesophageal reflux disease (GERD), hiatal hernia, obesity, and smoking [12, 13]. Male sex and age are also considered risk factors for GEJ adenocarcinoma although the incidence of the disease in females and males differs between types according to the Siewert classification (male to female ratio was 10.7 in type I, 4.9 in type II, and 2.2 in type III) [14].

The exact definition of GEJ cancers is not only of epidemiological importance. GEJ cancers have a different biology and prognosis than esophageal and gastric cancers. Differentiation also occurs within GEJ cancers; it is known that Siewert II and III cancers have a better prognosis than Siewert I [15]. GEJ cancers are characterized by high aggressiveness, and due to their localization, rapid systemic spread in both the thoracic and abdominal cavities. The disease is usually diagnosed at an advanced stage.

Gastric cancer

Gastric cancer (GC) is the fifth most common cancer in the world and the third leading cause of cancer-related deaths [16]. Men are affected about 2 times more often than women.

Gastric cancer-related morbidity and mortality vary widely by geographic region, but there has been a reduction in incidence worldwide over the last 50 years. These changes are attributed to the increased availability of fresh fruit and vegetables and the reduction in the consumption of pickled vegetables and smoked meat [17]. As many as 90% of GC cases (excluding cardia) can be attributed to *Helicobacter pylori* infections. While advances in the prevention and treatment of *H. pylori* infection have reduced the overall incidence of GC, they have also contributed to an increase in the incidence of cardia carcinoma (approximately a 7-fold increase in recent decades) [18].

A better understanding of the etiology and risk factors may help to reach a consensus on the approach to *H. pylori* infection. Dietary modification, smoking cessation, reducing alcohol consumption, and exercise currently appear to be the most effective ways to prevent GC. Some countries (e.g. Japan, South Korea, Chile, and Venezuela) have introduced population screening programs. Such programs mainly include radiological examinations with contrast and endoscopy [19]. Attempts are also made to determine the pepsinogen serum level or serological tests for *H. pylori*, but this is a subject of controversy, and there is no evidence of the effectiveness of such methods.

People with a family history of GC or patients with invasive lobular breast cancer diagnosed before the age of 50 are recommended to undergo genetic testing for mutations in the *CDH1* gene, encoding E-cadherin, which significantly increases the risk of GC [20].

There are even suggestions that carriers of mutations in the *CDH1* gene should be referred for prophylactic gastrectomy. Lynch syndrome is also associated with increased risk of GC [21].

Determination of PD-L1 expression

Immune checkpoint proteins, especially programmed death-ligand 1 (PD-L1) and programmed death receptor-1 (PD-1), play a key role in regulating the intensity and duration of the immune response, preventing the development of autoimmunity. These proteins also play an important role in the evasion of the anticancer immune response by cancer cells [22]. The interaction of PD-L1 (on the tumor cell) and PD-1 (on the surface of cytotoxic T cells) leads to suppression of T cells. Excessive expression of PD-L1, observed in progression of many cancers, allows escape from immune surveillance. PD-1 or PD-L1 inhibitors can specifically block the interaction of PD-1 and PD-L1 and thereby enhance the host's antitumor immune response and inhibit tumor growth.

PD-L1 expression on tumor cells or antigen-presenting cells is a potential predictor of response to immunotherapy. This expression can be recognized and measured by various available diagnostic techniques, e.g. enzyme-linked immunosorbent assay (PD-L1-ELISA), western blot, and next-generation sequencing (NGS) [23]. Currently, a widely used, practical and economical approach is the determination of PD-L1 expression in the tumor by immunohistochemistry (IHC) [24].

In the pivotal studies with PD-1 or PD-L1 inhibitors, specific drugs were combined with dedicated diagnostic tests, assessing PD-L1 expression on cancer cells, immune cells in the tumor stroma, or both. Several IHC assays are currently available to determine PD-L1 expression. Most of them have been developed as companion diagnostic tests for treatment in clinical trials. The assays use unique antibodies (22C3, 28-8, SP263, SP142) and staining platforms (Dako and Ventana), as well as different scoring methods and different clinical thresholds to determine PD-L1 positive expression [25]. Due to this variability, as well as the high variability of PD-L1 expression in different tumors, some controversy regarding the predictive value of the PD-L1 assay has arisen. In some cancers, a high inter-assay agreement has been shown, which could suggest that they can be used interchangeably, but this is currently not widely recommended. The development of a homogeneous, clinically significant, and reproducible method of PD-L1 assessment is crucial for identifying patients for treatment with PD-1/PD-L1 inhibitors, as it can significantly reduce the cost of diagnosis and shorten turnaround time [26, 27].

Tumor cells that show membrane staining of any intensity are considered PD-L1-positive. In tumor-associated immune cells, both membrane and cytoplasmic staining are considered positive [28].

In studies of patients with non-small cell lung cancer (NSCLC), the IHC 22C3 test was used to calculate the percentage of stained tumor cells (TPS, tumor proportion score) [29]. Tumor-infiltrating immunocompetent cells were not included in these assays. The TPS is calculated based on the number of PD-L1-positive tumor cells divided by the total number of all viable tumor cells multiplied by 100. Determining PD-L1 expression on tumor cells is also referred to as the tumor cell (TC) index, which also means the percentage of PD-L1-positive tumor cells related to all viable tumor cells on the slide [30].

In subsequent studies, in patients with GC and other cancers, TPS/TC turned out to be less effective in identifying treatment responders. Moreover, PD-L1 staining on both tumor cells and stromal immunocompetent cells has been shown to correlate better with treatment response in some cancers. Therefore, a method was developed to assess the expression of PD-L1 on both cell types in one area. This method of assessment was called a combined positive score (CPS) and allows the quantification of cancer and immune cells in one assessment [31]. The total positivity is calculated by the number of PD-L1-positive cells, including cancer cells, lymphocytes, and macrophages divided by the total number of viable cancer cells multiplied by 100. Thus, for the CPS, a score greater than 100 can be obtained.

The third method evaluates PD-L1 expression only in tumor-infiltrating immune cells (IC) — lymphocytes, macrophages, granulocytes, dendritic cells, or plasma cells, as a percentage of the tumor area with PD-L1 positive cells of any intensity. The latter assessment method is not used in the diagnosis of patients with gastrointestinal cancers. The described differences are presented graphically in Figures 1 and 2 [32, 33].

Immunotherapy in the treatment of patients with esophageal, gastroesophageal junction, and gastric cancer

Historically, advanced esophageal and gastric cancers were treated in the same way. For this reason, a diverse population of patients diagnosed with ESCC, EAC, GEJ, and GC was included in clinical trials with immunotherapy. The analysis of the results of these studies is difficult and makes the overall picture of immunological treatment seem extremely complicated. For this reason, it is also not possible to discuss the results of clinical trials for esophageal and gastric cancer immunotherapy

separately. In order to systematize the topic, clinical trials concerning mainly ESCC will be discussed separately. Clinical trials relating to GC but also trials that recruited patients with EAC and GEJ will be described separately.

Immunotherapy in the treatment of esophageal cancer

The CheckMate 648 study included 970 previously untreated patients with locally advanced, recurrent, or metastatic ESCC. Patients, regardless of PD-L1 expression, were randomly assigned to those treatment groups: nivolumab (240 mg every 2 weeks) with chemotherapy (cisplatin 80 mg/m^2 day 1, 5-fluorouracil 800 mg/m^2 day 1–5); nivolumab (3 mg/kg bw every 2 weeks) with ipilimumab (1 mg/kg bw every 6 weeks), or chemotherapy alone in the above scheme. In 49% of patients, PD-L1 expression on cancer cells was ≥ 1% [34].

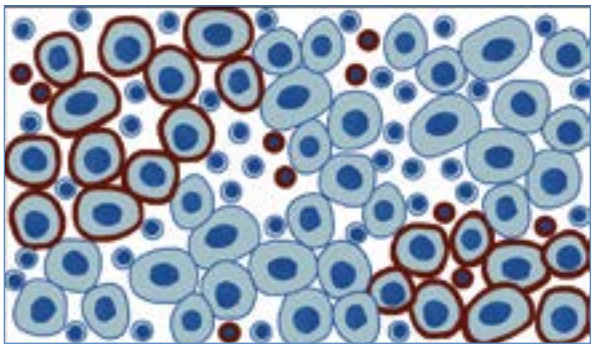

Figure 1. Schematic determination of PD-L1 (*programmed death-ligand* 1) expression on tumor cells (large cells with membrane staining) and tumor-infiltrating immunocompetent cells (small cells with membrane and cytoplasmic staining) [32]

The combination of nivolumab with chemotherapy significantly prolonged median overall survival (OS) compared to chemotherapy alone (13.2 *vs.* 10.7 months) and reduced the risk of death [hazard ratio (HR) = 0.74; 95% confidence interval (CI) 0.58–0.96] in the entire study population. The greatest benefit was achieved in the subgroup of patients with PD-L1 expression ≥ 1% (15.4 *vs.* 9.1 months, respectively, HR = 0.54; 95% CI 0.37–0.80). The use of nivolumab combined with ipilimumab compared to chemotherapy also resulted in significantly longer median OS (12.7 *vs.* 10.7 months) and a reduced risk of death (HR = 0.78; 95% CI 0.62–0.98) in the total population and in the subgroup with PD-L1 expression ≥ 1% (13.7 *vs.* 9.1 months, respectively; HR = 0.64; 95% CI 0.46–0.90). At the same time, immunotherapy alone was associated with a higher risk of primary treatment resistance, early progression, and death [35]. The objective response rate (ORR) was highest in the nivolumab plus chemotherapy subgroup compared to combination immunotherapy and chemotherapy alone (53%, 35%, and 20%, respectively). There was no benefit from immunotherapy in terms of PFS and OS in patients without PD-L1 expression. A retrospective analysis of treatment results based on the CPS index was also performed. The majority of patients (824 of 906) had a CPS ≥ 1. The best results were achieved in the CPS ≥ 10 subgroup. Grade 3 and 4 adverse events were more common in the nivolumab/chemotherapy group compared to chemotherapy and combination immunotherapy (47% *vs.* 36% *vs.* 32%, respectively)

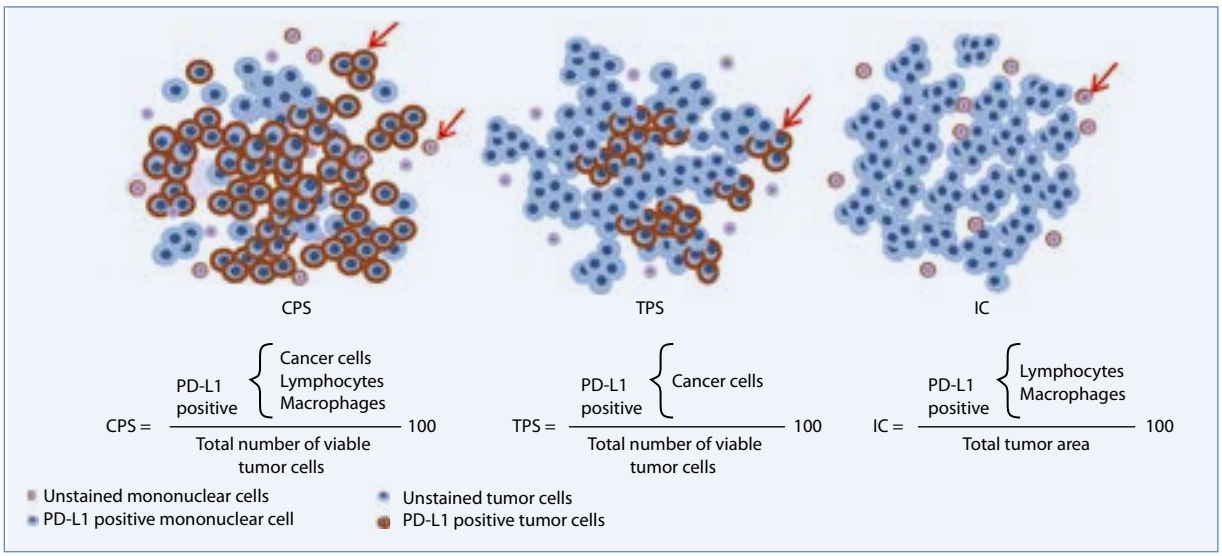

Figure 2. Methods of calculating programmed death-ligand 1 (PD-L1) expression indices — cumulative positive CPS, percentage of stained tumor cells (TPS) and tumor-infiltrating immune cells (IC) [33]; CPS — combined positive score; TPS — tumor proportion score (percentage of stained tumor cells); IC — immune cells (tumor-infiltrating immune cells)

and also were more likely to lead to treatment discontinuation (34% *vs.* 19% *vs.* 8%, respectively). This may be related to the fact that the duration of treatment with nivolumab and chemotherapy was the longest (5.7 *vs.* 3.4 *vs.* 2.8 months, respectively). Based on this study, two combination therapies — nivolumab in combination with ipilimumab and nivolumab in combination with fluoropyrimidine and platinum-based chemotherapy — have been approved by the European Medicines Agency (EMA) for the first-line treatment of patients with advanced, inoperable, relapsed or metastatic ESCC with tumor PD-L1 expression ≥ 1%. It should be mentioned that the US Food and Drug Administration (FDA) registered nivolumab in combination with ipilimumab or chemotherapy for the above-mentioned group of patients, regardless of PD-L1 expression.

Based on the KEYNOTE-590 study, pembrolizumab was registered in the treatment of esophageal cancer [36]. It included 749 previously untreated patients with locally advanced, recurrent, or metastatic esophageal cancer or GEJ (Siewert type 1), with a predominance of ESCC patients (73%). Patients were enrolled regardless of PD-L1 expression and randomly assigned to treatment with pembrolizumab (200 mg every 3 weeks for up to 2 years) with chemotherapy (cis-platinum 80 mg/m^2 day 1, 5-fluorouracil 800 mg/m^2 day 1–5 to 6 cycles) or chemotherapy alone. In 51% of patients, PD-L1 expression in tumor according to the CPS was ≥ 10. The CPS index was not a stratifying factor, however, subgroup analysis based on a CPS ≥ 10 was included in the statistical analysis.

The addition of immunotherapy significantly improved survival rates compared to chemotherapy alone with prolongation of median OS (from 9.8 to 12.4 months, HR = 0.73; 95% CI 0.62–0.83) and PFS (from 5.8 to 6.3 months, HR = 0.65, 95% CI 0.55–0.76). There was also an increase in the ORR (from 29 to 45%). The extension of median OS was driven mainly by ESCC patients (median OS 12.6 *vs.* 9.8 months, HR = 0.73; 95% CI 0.61–0.88), with the greatest benefit in patients with a CPS ≥ 10% (median OS 13.9 *vs.* 8.8 months, HR = 0.57; 95% CI 0.43–0.75). A smaller but significant gain was observed in all patients with a CPS ≥ 10%, regardless of histological type (median OS 13.5 *vs.* 9.4 months, HR = 0.64; 95% CI 0.51–0.80). The benefit of adding immunotherapy was not demonstrated in subgroups of patients with adenocarcinoma (HR = 0.74; 95% CI 0.54–1.02), ESCC with the CPS < 10 (HR = 0.99; 95% CI 0.74 –1.32), and all patients with CPS < 10 (HR = 0.86; 95% CI 0.68–1.10). The incidence of grade 3 and 4 adverse events was similar in both arms (86% in the study arm and 83% in the control arm).

Based on this study, pembrolizumab in combination with platinum-fluoropyrimidine-based chemotherapy has been approved by the EMA and is indicated for the first-line treatment of patients with unresectable or metastatic locally advanced esophageal cancer or human epidermal growth factor receptor 2 (HER-2) negative adenocarcinoma of the gastroesophageal junction, with a CPS ≥ 10. The FDA registered pembrolizumab in combination with chemotherapy for the above-mentioned group of patients, regardless of the CPS.

The effectiveness of immunotherapy in combination with chemotherapy in the first-line palliative treatment of ESCC patients has been confirmed by subsequent clinical trials using other anti-PD-1 molecules. The results of studies with camrelizumab, tislelizumab, sintilimab, and toripalimab in the Asian population were comparable to the results of previously presented studies [37–40]. The effectiveness of combining immunotherapy with platinum and paclitaxel-based chemotherapy has also been confirmed. The results of treatment effectiveness analyses depending on PD-L1 expression prevented unambiguous interpretation.

Immunotherapy can also be used at a later stage of palliative treatment. The phase III KEYNOTE-181 study was conducted in a group of 628 patients with locally advanced, inoperable, or metastatic ESCC (64%), EAC, and GEJ cancers (Siewert type I) regardless of PD-L1 expression (35% of patients had a CPS ≥ 10) with progression after first-line treatment. Patients were randomly assigned to treatment with pembrolizumab (200 mg every 3 weeks for up to 2 years) or single-agent chemotherapy (irinotecan, paclitaxel, or docetaxel) [41]. The result of the study was negative — no advantage of immunotherapy over chemotherapy in terms of OS in the general population was demonstrated. However, median OS was prolonged in an unplanned and retrospective subgroup analysis of ESCC patients with a CPS ≥ 10 (9.3 *vs.* 6.7 months in the chemotherapy group, HR = 0.64; 95% CI 0.46–0.90) with an over 2-fold increase of the 12-month survival rate (43% *vs.* 20%, respectively). The superiority of pembrolizumab was not demonstrated in the subgroup of patients with adenocarcinoma and ESCC with a CPS < 10. Fewer severe adverse events were observed in patients treated with pembrolizumab — 18% *vs.* 41%.

Pembrolizumab has not been registered by the EMA, while the FDA has registered the drug for the second and subsequent treatment lines in patients with advanced or metastatic ESCC with PD-L1 expression (CPS ≥ 10). According to the recommendations of the European Society for Medical Oncology (ESMO), pembrolizumab may be an option in this subgroup of patients if they have not previously received immunotherapy.

In the phase III ATTRACTION-3 study, treatment with nivolumab (240 mg every 2 weeks) was compared with single-agent chemotherapy (docetaxel or paclitaxel) in patients with locally advanced unresectable or metastatic ESCC with progression after at least one treatment line with platinum and fluoropyrimidine. The patients were qualified regardless of PD-L1 expression

(≥ 1% in about half of the patients) [42]. The use of nivolumab was associated with prolonged median OS compared to chemotherapy (10.9 *vs.* 8.4 months, HR = 0.77; 95% CI 0.62–0.96), almost doubling the 3-year survival rate — 15.3% *vs.* 8.7%, and a lower incidence of serious adverse events – 18% *vs.* 63%. PD-L1 expression had no impact on the effectiveness of immunotherapy, and the analysis of the CPS was not presented [43].

Based on these results, nivolumab in monotherapy was registered by the EMA and the FDA for the treatment of patients with advanced unresectable, recurrent, or metastatic ESCC after previous combination chemotherapy based on fluoropyrimidines and platinum.

The first positive results regarding the radical treatment of this disease have also been published, and further prospective clinical trials are ongoing. The result of the CheckMate 577 study showed the effectiveness of nivolumab in the adjuvant treatment of patients with esophageal cancer with residual disease after previous radiochemotherapy [44]. The study included 794 patients with esophageal (60%) or GEJ (40%) cancer; 30% were patients with squamous cell carcinoma. Patients were randomized to treatment with nivolumab (240 mg every 2 weeks for 1 year) or placebo. The primary endpoint of the study was disease-free survival (DFS). The use of nivolumab resulted in a doubling of median DFS (22.4 *vs.* 11 months, HR = 0.69; 95% CI 0.56–0.86). Only 9% of patients did not complete the one-year treatment with immunotherapy due to adverse events. The treatment benefit was independent of histopathology type, tumor location, and PD-L1 expression. Due to the too-short follow-up period and the required number of events not being met, data on OS are missing.

Both the EMA and the FDA have registered nivolumab for the adjuvant treatment in patients with esophageal or gastroesophageal junction cancer, with residual disease, after previous neoadjuvant radiochemotherapy and surgery. A study using immunotherapy after radical radiochemotherapy in patients with squamous cell esophageal cancer is ongoing (KEYNOTE-975, NCT04210115).

Immunotherapy in the treatment of patients with advanced gastric cancer

The clinical effect and safety of nivolumab in the first-line treatment of patients with advanced adenocarcinoma of the upper gastrointestinal tract (GC 69%, GEJ 18%, and EAC 12%) were assessed in the three-arm CheckMate 649 study involving 2031 patients randomly assigned to nivolumab in combination with FOLFOX/XELOX chemotherapy, chemotherapy, or combined immunotherapy with nivolumab and ipilimumab [45]. HER2 overexpression was an exclusion criterion. Patients were eligible for the study regardless of PD-L1 expression, which was the stratifying factor (PD-L1 ≥ 1% *vs*. PD-L1 < 1%). The endpoints included PFS and OS in the subgroup of patients with CPS ≥ 5 (60% of the total study population). The study was positive for both endpoints. The addition of nivolumab to chemotherapy in patients with a CPS ≥ 5 was associated with an increase in median PFS from 6 to 7.7 months (HR = 0.68; 95% CI 0.56–0.81) and median OS from 11.1 to 14 .4 months (HR = 0.70; 95% CI 0.61–0.81). This translated into an increase in the 2-year survival rate from 19% to 31%. In the total patient population, median OS was prolonged from 11.6 to 13.8 months (HR = 0.79; 95% CI 0.71–0.88). However, an unplanned subgroup analysis showed no benefit of adding immunotherapy in the subgroup with a CPS < 5 (median OS 12.4 *vs.* 12.3 months; HR = 0.94; 95% CI 0.79–1.11) and a CPS <10 (median OS 12.4 *vs.* 12.5 months; HR = 0.91; 95% CI 0.78–1.06). Treatment with immunotherapy alone, compared to chemotherapy, did not increase median OS in the total study population or in the subgroup with a CPS ≥ 5. The safety profile of the therapies used did not differ significantly from those known from previous studies. Treatment-related grade 3 or 4 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred in 60% of patients treated with nivolumab in combination with chemotherapy, 45% of patients receiving chemotherapy alone, and 38% of patients treated with immunotherapy alone, and the treatment discontinuation rate due to AEs was 38%, 26%, and 22%, respectively [46]. Based on this study, the EMA registered nivolumab in combination with chemotherapy based on fluoropyrimidines and platinum derivatives for the first-line treatment in patients with HER-2 negative, advanced or metastatic EAC, GEJ cancer or GC with PD-L1 expression CPS ≥ 5. The FDA approved nivolumab for the same indication regardless of PD-L1 expression.

The effectiveness of the combination of CAPOX/SOX chemotherapy with nivolumab was also assessed in the ATTRACTION-4 study with Asian patients diagnosed with unresectable, advanced, or recurrent, HER2--negative GC, or GEJ cancer [47]. The use of chemoimmunotherapy compared to chemotherapy alone led to an increase in median PFS (10.4 *vs.* 8.3 months; HR = 0.68; 95% CI 0.51–0.90), with no impact on OS. Positive PD-L1 expression was not an inclusion criterion. PD-L1 expression was assessed only on tumor cells, and the TPS did not influence the obtained results. The analysis based on the CPS was not included in the statistical plan of the study. This may suggest that in adenocarcinomas of the upper gastrointestinal tract, the TPS/TC index is less effective than the CPS in identifying patients responding to treatment.

The effect of pembrolizumab in the first-line treatment of patients with advanced GEJ cancer or GC was also evaluated in the KEYNOTE-062 study, in which 763 patients with a CPS ≥ 1 were randomized to pembrolizumab in monotherapy, in combination with

chemotherapy (cisplatin + 5Fu/capecitabine), or chemotherapy alone [48]. The primary endpoint was OS and PFS in patients with a CPS ≥ 1 or a CPS ≥ 10. The use of pembrolizumab alone resulted in comparable median OS in patients with a CPS ≥ 1 (10.6 *vs.* 11.1 months) compared to chemotherapy alone (10.6 *vs.* 11.1 months; HR = 0.91; 95% CI 0.74–1.10) and longer median OS in patients with a CPS ≥ 10 (37% of the total population) (17.4 *vs.* 10.8 months, respectively; HR = 0.69; 95% CI 0.49–0.97). These relations were not analyzed for statistical significance, as the study plan assumed a prior positive effect of chemoimmunotherapy, which was not achieved. The combination of pembrolizumab with chemotherapy compared to chemotherapy alone did not improve median OS in patients with a CPS ≥ 1 (12.5 *vs.* 11.1 months; HR = 0.85; 95% CI 0.70–1.03) nor with a CPS ≥ 10 (12.3 *vs.* 10.8 months; HR = 0.85; 95% CI 0.62–1.17). Interpretation of the results of this study is difficult in the context of the positive result of the CheckMate 649 study, which was conducted in a similar population. The differences may be the result of several factors, including the use of different chemotherapy regimens in these studies, a higher percentage of patients receiving second-line immunotherapy in the KEYNOTE-062 study, and finally, a high percentage of patients with a CPS ≥ 5 (60%) and a CPS ≥ 10 (48.5%) in the CheckMate 649 population compared to the patients with a CPS ≥ 10 in KEYNOTE-062 population (37%). This may indicate some kind of favorable sample selection in the CheckMate 649 study, as the assumptions of the statistical plan of the study based on analyses of similar populations assumed that the percentage (CPS ≥ 5) would be approximately 35%. Finally, the number of patients in the CheckMate 649 study was almost 3-fold higher compared to the KEYNOTE-062 study, which affected the statistical power and allowed the authors to show even small differences in the treatment effect.

Unlike anti-PD1 antibodies, the effectiveness of antibodies directed against the ligand of PD-1 in the treatment of gastric cancer has not been confirmed. In the Javelin Gastric 100 study, maintenance treatment with avelumab after first-line chemotherapy in patients with advanced, inoperable, HER-2 negative GEJ cancer or GC was evaluated [49]. No OS benefit was demonstrated (median OS was 10.4 months for avelumab and 10.9 months for chemotherapy alone) although the 24-month survival rate was higher in the avelumab group (22.1% *vs.* 15.5%). Avelumab used in the third treatment line (Javelin Gastric 300) was also not more effective than chemotherapy of the investigator's choice [50].

Pembrolizumab and nivolumab were also evaluated in subsequent treatment lines. The KEYNOTE-061 study compared pembrolizumab and paclitaxel in patients (n = 395) with advanced GEJ adenocarcinoma and GC, with PD-L1 expression CPS ≥ 1, with disease progression after first-line treatment based on a combination of platinum and fluoropyrimidine [51]. The primary endpoint was overall survival and progression-free survival in PD-L1-positive patients (CPS ≥ 1). The use of pembrolizumab in the subsequent treatment line compared to paclitaxel was associated with a similar ORR (16 *vs.* 14%), significantly shorter median PFS (1.5 *vs.* 4.1 months, respectively; HR = 1.27; 95% CI 1.03–1.57), and no effect on median OS (9.1 *vs.* 8.3 months, respectively; HR = 0.82; 95% CI 0.66–1.03). Post-hoc analyses after 24 months of follow-up showed a significantly longer duration of response in the pembrolizumab arm (19.1 *vs.* 5.2 months for paclitaxel) and a doubling of the 2-year survival rate (19.9% *vs.* 8.5%). The results of the retrospective analysis showed that the greatest clinical benefit was achieved in the subgroups of patients with a CPS ≥ 5 and a CPS ≥ 10. The results of this study did not change clinical practice.

Nivolumab used in the third and subsequent treatment lines in patients with unresectable, recurrent GEJ cancer or GC turned out to be more effective than placebo [52]. In the ATTRACTION-2 randomized study in an Asian population, the ORR was reported only in patients treated with nivolumab (11.2%). The median duration of response was relatively long (9.53 months), resulting in a slight prolongation of median OS compared to placebo (5.26 *vs.* 4.14 months, respectively; HR = 0.63; 95% CI 0.51–0.78). Similar results were obtained with pembrolizumab used in subsequent lines. In the one-arm KEYNOTE-059 study with 259 patients, the ORR was 11.6% with a median duration of response of 8.4 months, with better outcomes in PD-L1 positive patients (15.5% and 16.3 months, respectively) [53].

It is difficult to draw solid conclusions from the results of these two studies. The use of placebo in the control group (ATTRACTION-2) or the lack of a control group (KEYNOTE-059) raises the question of whether immunotherapy would be more effective than classic cytotoxic drugs in this clinical situation. ESMO guidelines do not recommend the use of immunotherapy in subsequent treatment lines in unselected populations.

Microsatellite instability (MSI), a phenotypic reflection of mismatch repair deficiency (dMMR), is found in approximately 10% of gastric cancer patients. dMMR/MSI cancer is found more often in patients with stages I and II and the elderly. In the group of patients over 85 years of age, dMMR/MSI can account for 48% of cases [54–57]. In advanced disease, the percentage of dMMR/MSI tumors is estimated at 3–7%. Retrospective analyses of the previously described clinical trials have shown that this selected group may benefit incomparably more from the use of immunotherapy [54]. In the KEYNOTE-062 study, dMMR/MSI patients (7.3% of the total population) treated with pembrolizumab had a 2-fold higher ORR of 65% compared to 37% in patients treated with chemotherapy alone.

The median duration of response was 21.2 months in this subgroup and median OS was not reached. The 2-year survival rate was 71% for pembrolizumab, 65% for the combination of pembrolizumab with chemotherapy, and 26% for chemotherapy alone [54]. These data suggest that in dMMR/MSI patients, there is no benefit from adding chemotherapy to immune therapy.

In the CheckMate 649 study, despite the disappointing results of treatment with immunotherapy alone (nivolumab with ipilimumab), dMMR/MSI patients (3% of the total population) seem to benefit the most from this therapy. Combination immunotherapy was associated with an ORR of 70% compared with 55% for chemoimmunotherapy. Median OS for the combination of nivolumab and ipilimumab was not reached (HR = 0.28; 95% CI 0.08–0.92) while for the combination of chemotherapy and nivolumab it was 38.7 months and for chemotherapy alone 12.3 months (HR = 0.38; 95% CI 0.17–0.84). The benefit was observed regardless of the CPS value [45].

Immunotherapy in patients with dMMR/MSI GEJ cancer and GC is also active in further treatment lines. The ORR for pembrolizumab was 46% (*vs.* 16% for chemotherapy) in the KEYNOTE-061 study (5.3% of dMMR/MSI patients), and 57.1% in the KEYNOTE-059 study (4% of dMMR/MSI patients). Median PFS and OS in dMMR/MSI patients treated with pembrolizumab were not reached in both studies, and the 12-month survival rates were 71% and 73%, respectively [54]. Pembrolizumab immunotherapy has been registered by the EMA for the treatment of patients with unresectable or metastatic dMMR/MSI GC after failure of at least one treatment line. Treatment with immunotherapy without chemotherapy in patients with dMMR/MSI gastric cancer has not yet been registered as the first-line treatment and is not recommended.

The value of immunotherapy in the earlier stages of MSI/dMMR GC was demonstrated in a phase II study, in which a 12-week neoadjuvant treatment with nivolumab and ipilimumab resulted in pathomorphological complete response in 58.6% of operated patients [55].

New therapeutic options based on combining immune checkpoint inhibitors with targeted therapy

The positive effects of using trastuzumab in the treatment of patients with advanced GC with HER2 overexpression became the basis for the concept of combining anti-HER2 therapy with immunotherapy and chemotherapy. In the KEYNOTE-811 study, a triple combination of trastuzumab with chemotherapy and pembrolizumab/placebo was evaluated. The first interim analyses show a higher ORR (74.4% in the pembrolizumab arm *vs.* 51.9% in the placebo arm), complete remission rate (11.3% *vs.* 3.1%, respectively), and disease control rate (95% *vs.* 89.3%) [58, 59].

The INTEGA study evaluates the effect of combining trastuzumab with nivolumab and ipilimumab in relation to nivolumab combined with trastuzumab and FOLFOX chemotherapy in patients with HER2-positive, advanced GEJ adenocarcinoma and GC [60]. Preliminary data suggest a prolongation of median PFS and OS with chemotherapy compared to the combination of immunotherapy and anti-HER2 treatment (median PFS 10.7 *vs.* 3.2 months, median OS 21.8 *vs.* 16.4 months) [61]. The ongoing (enrollment phase) DESTINY-GASTRIC 03 study is evaluating the role of trastuzumab deruxtecan in patients progressing on trastuzumab (Part 1) or previously untreated with anti-HER2 therapy (Part 2). An interesting concept is also the combination of immune checkpoint inhibitors with ramucirumab, which blocks *Vascular endothelial growth factor receptor 2* (VEGFR2). The effect of such a combination is increasing the expression of PD-L1, increasing the infiltration of the tumor microenvironment by CD8+ T cells, and inhibiting the function of regulatory T lymphocytes responsible for immunosuppressive phenotype [62]. The clinical effect and safety of the combination of ramucirumab and pembrolizumab in the first-line treatment of patients with advanced GEJ adenocarcinoma or GC was assessed in the JVDF study [63]. The primary endpoint was the safety of combination therapy and the secondary endpoints were PFS, OS, and ORR. Median OS in the population of 28 patients included in the study was 14.6 months and was longer in the group of patients expressing PD-L1 (17.3 months in PD-L1 positive patients *vs.* 11.3 months in PD-L1 negative patients). A similar relationship also concerned PFS, whose median in the general population was 5.6 months (8.6 months in PD-L1 positive patients *vs.* 4.3 months in PD-L1 negative patients). Treatment-related grade 3 adverse events according to the CTCAE were reported in 18 patients, with hypertension (14%) and transaminase elevation (11%) being the most common. Importantly, none of the patients had CTCAE grade 4 or 5 complications.

Conclusions

Immunotherapy has significantly changed the treatment strategy for patients with ESCC, EAC, GEJ cancer, and GC. This was reflected in the international expert recommendations of the ESMO and National Comprehensive Cancer Network (NCCN). The number of presented studies and their results show how complicated this topic is and how many aspects still need to be explained. Figures 3 and 4 present the up-to-date knowledge regarding first-line and subsequent-line

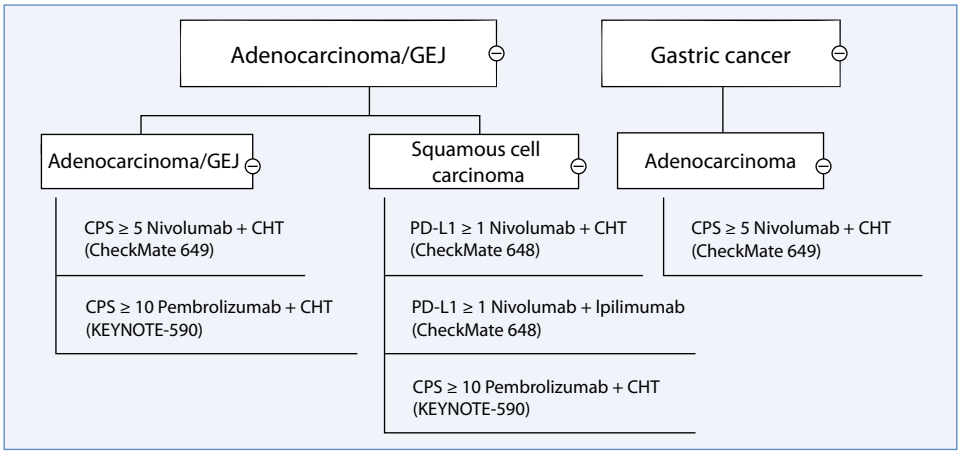

Figure 3. Immunotherapy of esophageal and gastric cancer — the first line of systemic treatment; GEJ — gastroesophageal junction; CPS — combined positive score; CHT — chemotherapy; PD-L1 — programmed death-ligand 1

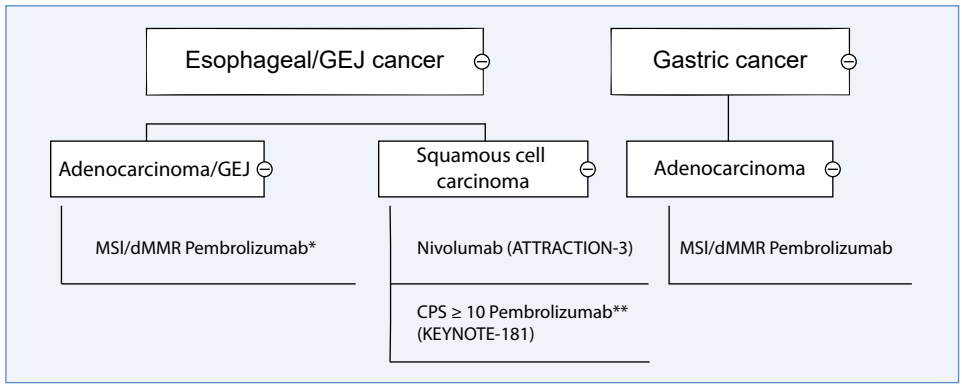

Figure 4. Immunotherapy of esophageal and gastric cancer — the second and subsequent lines of systemic treatment; *No EMA registration, recommended by ESMO; **No EMA registration, recommended by ESMO as an option; GEJ — gastroesophageal junction; MSI — microsatellite instability; dMMR — mismatch repair deficient; CPS — combined positive score.

treatments with immunotherapy of advanced esophageal and gastric cancer based on EMA registered indications and ESMO recommendations. Many interesting studies are still ongoing, which may lead to further changes in the guidelines.

Conflict of interest

M.G.: received remuneration from Merck, Amgen, BMS, MSD, and Servier, unrelated to the article.

B.R.: received remuneration from Merck, Amgen, BMS, MSD, and Servier, unrelated to the article.

M.K., W.R.: declare no conflict of interest.

T.K.: received honoraria from Roche, MSD, and BMS, unrelated to the article.

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REVIEW ARTICLE

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Optimization of diagnostic and therapeutic management in patients with stage III non-small cell lung cancer — experience of the centers in Poznań

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ABSTRACT

Lung cancer is one of the most frequently diagnosed malignancies, with one of the worst prognoses. Non-small cell lung cancer (NSCLC) is the dominant histological type, accounting for 85% of cases. In Poland, in more than one-third of patients, NSCLC is diagnosed at stage III. One of the most effective methods of radical treatment in such cases is concurrent radiochemotherapy. However, in Poland the percentage of patients eligible for this type of therapy is quite low, due to delayed diagnosis, lack of reference centers, long qualification process for treatment, and ineffective treatment organization. This article discusses the optimization of therapeutic management in patients with stage III NSCLC based on the experience of centers in Poznań (the Greater Poland Cancer Center and Greater Poland Center for Pulmonology and Thoracic Surgery). Some modifications include introduction of a surgery qualification form, urgent early evaluation using combined positron emission tomography (PET)/computed tomography (CT) and invasive mediastinum evaluation, and initial qualification for radiochemotherapy (with the setting of dates) already during diagnostics. These activities led to the multiplication of the number of patients qualified for concurrent radiochemotherapy.

Key words: non-small cell lung cancer, radiochemotherapy, concurrent radiochemotherapy, sequential radiochemotherapy, multidisciplinary team, durvalumab

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Introduction

Lung cancer is one of the most frequently diagnosed malignant neoplasms in Poland and the leading cause of cancer-related deaths in both sexes [1]. More than 20000 lung cancer cases are diagnosed annually, with non-small cell lung cancer (NSCLC) being the most common subtype (approximately 85%) [2, 3].

In Poland, in approximately 35% of patients, NSCLC is diagnosed at stage III (in most cases this is an inoperable stage), and this percentage is higher than in some countries [4, 5]. According to the 2016 data from

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the American Cancer Society, the 5-year survival rate of patients with NSCLC in stages IIIA and IIIB was 14% and 5%, respectively [6].

According to the recommendations for chest neoplasms treatment issued by the Polish Society of Clinical Oncology, in patients with stage III NSCLC ineligible for surgery, concurrent (cCRT) or sequential chemoradiotherapy (sCRT), chemotherapy, or radiation therapy should be used. In the case of cCRT, the Polish guidelines recommend the use of consolidation treatment with durvalumab for 12 months [4]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with inoperable stage III NSCLC should be treated with cCRT with consolidation therapy with durvalumab [7]. Although it is one of the most effective methods of radical treatment, in Poland the percentage of patients eligible for this treatment is quite low [8]. By comparison, in the United States and the United Kingdom, approximately 50% of patients with stage III NSCLC receive cCRT [9, 10].

There is a possibility of increasing the cCRT use in Polish centers, as evidenced by data from Poznań centers — the Greater Poland Cancer Center (WCO, Wielkopolskie Centrum Onkologii) and the Wielkopolska Center of Pulmonology and Thoracic Surgery (WCPiT, Wielkopolskie Centrum Pulmonologii i Torakochirurgii). The solutions implemented by WCO and WCPiT contributed to a significant increase in the number of patients qualified for cCRT (from 12 in both 2018 and 2019 and 2 in the first half of 2020 to 30 in 2021) and consolidation therapy (from 1 in 2020 to 12 in 2021). This article aims to discuss the methods of optimizing the management of patients with stage III NSCLC based on the experience of the WCO and WCPiT.

Treatment of stage III NSCLC

Qualification for surgical treatment of stage III NSCLC

The most important factors in qualifying patients for surgical treatment include the disease stage, histological type, general performance status (PS), and the presence of serious comorbidities [11]. Radical surgery may be considered for T3/T4 and N0/N1 tumors. Patients with N2 disease constitute a diverse group, requiring an individual treatment approach. In such cases, there is a very important role of the multidisciplinary team (thoracic surgeon, pneumonologist, medical oncologist, radiation oncologistradiation oncologist, and radiologist), which classifies the tumors into a group of potentially resectable, potentially resectable with possible incomplete resection, or inoperative [12]. Surgical treatment may be considered in patients with single metastases in mediastinal lymph nodes and pathologically proved complete mediastinal lymph nodes response following induction treatment, usually including chemotherapy or radiochemotherapy [4, 13]. The use of induction therapy facilitates or enables complete resection. A meta-analysis by Guo et al. [14] showed that the use of preoperative radiochemotherapy in patients with stage III NSCLC is associated with better local disease control and tumor shrinkage with complete pathological response compared with chemotherapy. However, no prolongation of progression-free survival or increase in 5-year survival rate was observed. On the other hand, the use of postoperative chemotherapy (with or without radiotherapy) significantly extends overall survival; chemotherapy is recommended in patients in good PS, without serious comorbidities, and with complete recovery after pulmonary resection [4].

During surgery planning in patients with NSCLC with limited N2 disease, it is crucial to perform staging using minimally-invasive methods. The European Society of Thoracic Surgeons (ESTS) guidelines regarding the pre-operative mediastinal lymph nodes assessment recommend that computed tomography (CT), positron emission tomography (PET), or combined PET-CT should be performed first. Patients with no distant metastases (M0) and lymph node involvement (N0) are eligible for resection. In patients with N1 disease, a centrally located tumor or tumor larger than 3 centimeters in diameter, invasive examinations should be performed including evaluation and biopsy of mediastinal lymph nodes during endobronchial ultrasound (EBUS), esophagal ultrasonography (EUS), or video-assisted mediastinoscopy (VAM) due to a significantly higher risk of radiologically silent N2 disease. If the case of N2 disease suspected in radiological examinations, the aforementioned invasive diagnostic methods are the standard of care. In both situations, surgical treatment is used after exclusion of N2 disease [4, 12].

In a survey on the management of patients with N2 disease conducted by the NCCN, approximately 90% of respondents declared that radical surgery should be considered in the case of involvement of one lymph node smaller than 3 centimeters in diameter, while almost 48% of physicians declared that radical surgery should be considered in the case of N2 involvement of more than one lymph node if none of them exceeds 3 centimeters. In addition, 80% of physicians performed an initial assessment of the mediastinal lymph node with the use of EBUS/EUS [7].

The data regarding the number of NSCLC patients undergoing lung resection in WCPiT in 2016–2019 indicate that each year about 20% of patients had stage IIIA cancer, while in half of them, IIIAN2 tumor was diagnosed postoperatively (10%). By comparison, according to the nationwide data from the National Lung Cancer Database, stage IIIA NSCLC accounted for approximately 14% of all operated tumors [15].

Radiochemotherapy

A combination of radiotherapy with chemotherapy is more effective than radiation alone, and cCRT is associated with better outcomes than sequential treatment [4, 16]. In patients with inoperable stage III NSCLC in good general condition, with a slight decrease in body weight, adequate respiratory capacity, and limited tumor burden, the use of cCRT is recommended. In the case of contraindications to cCRT, the use of sCRT should be considered [12].

Radiation therapy alone in patients with locally advanced tumors is associated with poor outcomes due to the high risk of distant metastases. Chemotherapy improves the local effectiveness of radiotherapy through the radiosensitizing effect (it mainly concerns platinum derivatives) and reduces the risk of blood-borne dissemination [16]. A meta-analysis of phase III trials showed that combined radiotherapy and chemotherapy reduce the risk of death by 13% and increase the 2-year survival rate by 4% compared to radiation alone [17]. Sequential radiochemotherapy also led to an increase in the 5-year overall survival rate from about 5% to 10% compared to radiotherapy alone, and concurrent use of both methods increases it to about 15% [16, 18]. Compared to sCRT, cCRT reduces the risk of death by 14% after two years and significantly reduces the risk of local progression [19, 20].

cCRT is associated with several times higher risk of acute (≥ grade 3) esophagitis and slightly more intense pneumo- and myelotoxicity than sCRT. Concurrent radiochemotherapy should, therefore, only be used in specialized centers capable of treating possible complications [21].

Patients eligible for radiochemotherapy (cCRT and sCRT) are in good performance status (ECOG 0–1), without significant weight loss (up to 10% of the ideal body weight during 3 preceding months), with limited tumor mass, adequate respiratory capacity, and without significant comorbidities. Patients over 70 years of age in a very good PS qualify for sCRT [4, 16, 22]. There are reports of concurrent therapy benefits in the elderly, but the evidence is still limited [23]. Age is not considered to be an absolute contraindication for cCRT, but a comprehensive geriatric evaluation should be performed, including the risk based on medical comorbidities and the patient's overall functioning.

Regimens of chemotherapy used as part of cCRT include:

— cisplatin at a dose of 75–100 mg/m^2 (day 1) with vinorelbine at a dose of 25–30 mg/m^2 (days 1 and 8) every 21 days;
— cisplatin at a dose of 75–100 mg/m^2 (day 1) with etoposide at a dose of 100–120 mg/m^2 (days 1, 2, and 3) every 21 days.

Sequential chemoradiotherapy can include either one of the above regimens or cisplatin in combination with docetaxel (75 mg/m^2 — day 1), paclitaxel (200 mg/m^2 — day 1) or gemcitabine (1000–1250 mg/m^2 — day 1 and 8). If cisplatin is contraindicated, carboplatin may be used (AUC 6 — day 1). Subsequent cycles of chemotherapy are administered every 21 days [4].

In NSCLC with other than predominantly squamous cell histology, pemetrexed (500 mg/m^2) based chemotherapy with either cisplatin (75 mg/m^2) or carboplatin (AUC 5) can be used [24–26].

In radical concurrent or sequentially radiochemotherapy, conventionally fractionated (1.8–2 Gy per day), conformal radiation at a total dose of 60–66 Gy is used [4, 12]. Irradiated area should include the primary tumor and the affected hilar and mediastinal lymph nodes. The development in radiotherapy and the possibility of using modern techniques allow for more precise determination of the area to be irradiated, toxicity reduction, and optimal escalation of the radiation dose [27, 28]. Interruptions during radiotherapy decrease treatment effectiveness and overall survival of patients receiving cCRT [29]. If the risk of severe radiotherapy complications is high in the opinion of the radiation oncologist, it is more favorable to qualify patients for sequential treatment to reduce the tumor volume during chemotherapy and to conduct radiotherapy in a safe manner.

In all patients qualified for radical treatment, pulmonary function tests (spirometry, gasometry) should be performed, as well as PET-CT and EBUS for evaluation of suspicious lymph nodes. Brain imaging should also be performed before radical treatment in every NSCLC patient. PET-CT examination has crucial importance in radiotherapy planning; meta-analysis results confirmed that in approximately 40% of NSCLC patients target radiotherapy area was significantly changed after PET-CT examination [30]. Another study found that the incorporation of PET into radiation planning can improve local control and reduce toxicity. Therefore, PET-CT imaging should become a standard of care in the radiotherapy planning process [31].

Consolidation treatment

Consolidation therapy with durvalumab, a monoclonal antibody against the programmed death-ligand 1 (PD-L1), significantly improved treatment outcomes in patients with unresectable stage III NSCLC after successful cCRT. Phase III PACIFIC studies showed that the survival rate in the group receiving durvalumab as consolidation treatment after 12 months from randomization was 83.1% *vs.* 74.6% in the placebo group, after 24 months — 66.3% *vs.* 55.3%, after 36 months — 56.7% *vs.* 43.6%, after 48 months — 49.6% *vs.* 36.3%

and after 60 months — 42.9% *vs.* 33.4%, respectively. In contrast, the percentage of patients achieving 12-month progression-free survival was 55.3% in the group receiving durvalumab as consolidation treatment *vs.* 34.4% in the placebo group, 24month progression free survival (PFS) — 44.8% *vs.* 24.8%, 36month PFS — 39.8 % *vs.* 20.5%, 48-month PFS — 35.3% *vs.* 19.5%, and 60-month PFS — 33.1% *vs.* 19.0%, respectively. The incidence of serious adverse events was similar in both groups [32–35].

Since January 2021, consolidation immunotherapy with durvalumab after cCRT in locally advanced NSCLC has been reimbursed under the B6 drug program [36]. Patients can be enrolled in the program without the need of PD-L1 expression assessment.

Optimization of treatment in stage III NSCLC patients

The estimates of the National Consultant indicate that in Poland cCRT is used in approximately 300 patients annually, which is at least 3 times less than the real number in need [37]. The reasons for insufficient use of cCRT include delayed lung cancer diagnosis, lack of reference centers, long process of qualification for treatment, and inefficient treatment organization together with service valuation.

In June 2020, a meeting of specialists from the WCO and WCPiT was organized, aimed at determining actions that could improve the management of stage III NSCLC patients. The individual aspects influencing the effectiveness of treatment in Poland are discussed below, and the solutions implemented in the WCO and WCPiT are presented, which have contributed to the improvement of stage III NSCLC treatment (including an increase in the number of patients receiving cCRT).

Late diagnosis of lung cancer

Lung cancer develops dynamically, and efficient diagnostics allows detection of the disease at the earliest possible stage. In Poland, patients are admitted to pulmonary departments with advanced cancer and often in poor general condition, which makes it impossible to qualify them for cCRT. Primary care physicians may play an important role as their activities may shorten the path from symptom onset to pulmonologist consultation. Activities should, therefore, include shortening the waiting time for a specialist appointment, performing screening tests, and increasing public awareness of lung cancer. Particular attention should be paid to the "at-risk" population (age over 55, current or former smokers). Currently, Poland is implementing the "National Program of Early Lung Cancer Detection Using Low Dose Computed Tomography". It initially covered 6 macroregions, including Poznań, and has recently been extended to the entire country [38]. The program is to last until 2023, and the number of participating institutions is constantly growing.

Extended process of qualification for treatment

The extended process of qualification for surgery, induction treatment or radiochemotherapy causes patients to be in a more advanced disease stage and worse general condition. Many patients may also require additional imaging tests, which is usually associated with a long turnaround time (TAT) in Polish centers, extension of the diagnostic process, and further delay in treatment initiation. At the WCO and WCPiT, a qualification form for surgery was introduced to assess possible contraindications to surgery during the tumor board and obtain a faster decision of the thoracic surgeon. Moreover, early simultaneous patient qualification for PET-CT and possibly EBUS/EUS, based on CT results, was recommended, which halved the waiting time for examinations and treatment initiation (from two months to a month). At the stage of qualifying for diagnostic tests, the council determines the earliest possible treatment date (adjusted to the dates of diagnostic tests and expected results). Additionally, the patient's general condition and accompanying diseases are analyzed during an interdisciplinary meeting to assess possible contraindications to radiotherapy and chemotherapy.

It should be emphasized that PET-CT examination in patients with stage III NSCLC should be performed routinely, especially in the case of doubts about the patient's eligibility for cCRT or sCRT. However, it is necessary to shorten the duration of diagnostics with imaging tests. According to the Alivia Foundation data, the average waiting time for CT in Poland is 28 days, for MRI — 52 days, and for PET-CT — 21 days [39]. The waiting time varies depending on the voivodship due to the uneven distribution of medical equipment and personnel. Importantly, complete diagnostic tests, along with the correct assessment of the disease stage, allow for quick and accurate treatment decisions during council meetings. At the centers in Poznań, each patient who is tentatively qualified for cCRT is urgently referred for PET-CT examination. Additionally, the date of the planned treatment determined during the council meeting influences the time of the examination.

Lack of reference centers with multidisciplinary teams

The lack of reference centers with multidisciplinary teams, including pneumonologists, oncologists, thoracic surgeons, radiation oncologist, radiologists,

or pathologists, is another important factor influencing the treatment outcomes in NSCLC patients. Studies have shown that cooperation between specialists in various fields enables the reduction of time from diagnosis to treatment implementation; it also results in increasing the overall survival rate and prolonged progression-free survival time [40]. The NCCN recommends that the lung tumor board discuss both the diagnostic and the treatment process [7]. If the center cannot use both treatment methods (chemotherapy and radiotherapy), it is crucial to strengthen cooperation between teams from different centers. At the WCO, a team of radiation oncologists dedicated to the treatment of lung cancer patients had already been established and now participates in the tumor board and then conducts radiotherapy.

In Poznań centers, NSCLC patients eligible for cCRT have become a priority group (similarly to potentially operable patients) for both specialist doctors and coordinators overseeing the diagnostic and therapeutic path. A pneumonologist refers patients to the tumor board that take place twice a week – it consists of a clinical oncologist, radiologist, radiation oncologist, and thoracic surgeon. During the meeting patients eligible for therapy are discussed, and instructions are given in the case of diagnostic difficulties, indicating the optimal way to establish a diagnosis and further management.

Treatment toxicity

As already mentioned, cCRT is associated with greater treatment toxicity compared to sCRT or radiotherapy alone, which is of concern for physicians and patients [41]. However, it has been shown that the number of side effects and toxicity grades depend on the type of radiotherapy and chemotherapy regimen [42, 43]. As part of the optimization of cCRT in the WCO and WCPiT, 2 cycles of chemotherapy consisting of cisplatin (75 mg/m^2 — day 1) and etoposide (100 mg/m^2 — day 1, 2, and 3) are administered in 21-day cycles as it was noticed that the vinorelbine-containing regimen resulted in significant hematological complications after the 8th day of the cycle. In addition, the modern 3D–4D conformal radiotherapy technique is used, which allows limiting the irradiation of healthy tissues due to precise assessment of tumor localization [44]. According to the guidelines, patients receive a total radiation dose of 60 Gy (2 Gy per fraction, 30 fractions). Granulocyte colony-stimulating factors are used prophylactically.

Organization of treatment

The organization of treatment of NSCLC patients in Poland is also a challenge. The number of centers where both radiotherapy and chemotherapy are available is limited and, therefore, until Lung Cancer Units are established, it is worth developing cooperation between pneumology and oncology departments. It should be noted that cCRT procedure also includes the treatment of possible complications, which is practically impossible in an outpatient setting.

Although the treatment of patients taking place in several centers is associated with certain difficulties (e.g. the need to organize patient transport), the centers in Poznań have proved that the willingness to cooperate allows for good treatment organization, even during the COVID-19 pandemic. For example, considering that group transport often places a heavy burden on cancer patients, weakened by disease and treatment, and increases the risk of infection (especially during the COVID-19 pandemic), it was decided to create special transporting teams. Additionally, patients undergoing cCRT are placed in the same room to limit their contact with other patients. Staff and patients are adequately equipped with personal protective equipment. For patient safety, mandatory tests for the presence of SARS-CoV-2 (performed every 7 days) have been introduced.

Initial results of optimization

In June 2020, a meeting of a team of specialists from Poznań was held to discuss methods of diagnosis and treatment results in patients with stage III NSCLC. The possibilities for improvement using currently available methods were assessed. Identifying the causes and determining the corrective and optimizing actions, which we have presented in this article, led to a significant increase in the number of patients qualified for cCRT, from 12 patients in both 2018 and 2019 and 2 patients in the first half of 2020 to 30 patients in 2021. Additionally, 12 patients were qualified for consolidation treatment with durvalumab last year. These data confirm the effectiveness of the new strategy and the possibility of a significant improvement in treatment outcomes in patients with stage III NSCLC.

Conclusions

There is a great need for improvement in the diagnosis and treatment of patients with stage III NSCLC in Poland to ensure they have access to cCRT with possible consolidation treatment. For this purpose, it is necessary to provide adequate training and optimize therapeutic procedures, including 1) education in the field of treatment options for patients with stage III NSCLC, 2) development of dedicated interdisciplinary teams (tumor boards) to establish management and treatment

regimens for patients with early and locally advanced NSCLC, 3) shortening the time of diagnostics by early consultation and qualification to PET-CT examination and, at the same time, for invasive mediastinum evaluation, and 4) prioritization of radical procedures by setting early treatment schedules.

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VIA MEDICA

REVIEW ARTICLE

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Male breast cancer: a budding and unaddressed issue

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ABSTRACT

Incidence of male breast carcinoma (MBC), although rare, recently has an increasing trend. The increase in incidence is associated with increasing age, and poor clinical outcome seen with MBC is mostly because of illiteracy and lack of health education and shyness in reporting to the clinical physician. In this context, a comprehensive review regarding this forth bursting clinical scenario is important. The present article focus on that aspect encompassing but not limited to different clinical studies. The randomized trials on MBC are sparse and most of the studies are retrospective in nature due to rarity of cases. MBC treatment line is derived from female breast cancer guidelines. MBC has a poorer prognosis than female breast cancer. MBC patients in India present in advanced stage and surgery remains challenging due to paucity of breast tissue. Post mastectomy radiation is indicated on the same lines as of female breast cancer and it decreases locoregional recurrence. Adjuvant hormonal therapy decreases recurrence and improves survival. Further clinical trials are required including large number of patients to study different parameters in respect of prognosis and survival.

Key words: breast, cancer, male, mastectomy, radiation

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Introduction

Male breast carcinoma (MBC), which is a relatively isolated phenomenon occurring in fewer than 1% of breast cancer cases in males, has been on the rise over the past two to three decades. The incidence of MBC increases with age and the median age at presentation in India is 57 years [1]. Risk factors include *BRCA1* and *2* mutations, Klinefelter syndrome, chronic testicular and liver disease, obesity, and alcohol intake [1]. Literature about male breast cancer, including randomized trials or retrospective series, is sparse, particularly in developing countries like India. Moreover, awareness about MBC in the general population is also very poor. There is an urgent need for collaborative trials and reviews from oncologists of different kinds to provide an evidence base for the most effective combination therapies for men with breast cancer.

Management of MBC is wholly derived from data on female breast cancer although there are some differences between breast cancer in males and females (Tab. 1 [2]). Literature suggests that MBC has a poor prognosis in comparison to female breast cancer [3, 4]. The paucity of breast tissue in males contributes to surgically poor adequate margins. Moreover, in India, most patients present in a locally advanced stage, which makes it even more difficult to achieve negative surgical margins. Hence adjuvant post-mastectomy radiotherapy (PMRT) is indicated as per female breast cancer guidelines. Post-mastectomy radiotherapy decreases locoregional recurrence (LRR) [5]. Chemotherapy and hormonal therapy are also given as per female breast cancer guidelines. Hormonal therapy has benefits in terms of fewer chances of recurrence and increased survival rates [1]. This article provides an in-depth review of male breast cancer regarding etiopathogenesis, diagnosis, and management in the Indian setting.

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Table 1. Differences between male and female breast cancer

	Male breast cancer	Female breast cancer
Incidence	Less common	More common
History of familial cancer	More common	Less common
Site	Central region	Upper outer quadrant
Nipple involvement	More common	Less common
Breast tissue	Less	More
Ducts and lobules	Few	More
Lobular carcinoma	Less common	More common
Age at diagnosis	6^{th} to 7^{th} decade	5^{th} to 6^{th} decade
Stage at presentation	Advanced	Early
High grade	More common: 85% grade 3 [2]	Less common: 50% grade 3 [2]
ER/PR expression	More than 95%	Less (60–70%)
HER2-neu overexpression	Less (2–15%)	More (18–20%)
Prognosis	Poor	Good
Surgery	Poor adequate margins due to paucity of breast tissue	Adequate margins possible
BCS	Less common	More common
Screening	Less common	More common
Trials	Less	More

BCS — breast conservative surgery; ER/PR — estrogen receptor/ progesterone receptor; HER — human epidermal growth factor receptor

Incidence

The approximate numbers of new cases of MBC are 1 in 100 000 in the US and Europe, < 5 in Japan, and may be 15% of all breast carcinoma cases in some parts of Africa [6]. The age-standardized incidence rate (ASR) is 0.4 per 100 000 in Mumbai in India. The incidence increases with age till 80 years, and then it reaches a plateau [7].

Etiopathogenesis and risk factors

Heredity, more precisely a positive family history, is the prime factor in occurrence of MBC. Breast or related cancers (like ovarian cancers) in a first-degree relative, irrespective of their sex, increase the risk of breast cancer in men from 2 to 5-fold. Breast cancer predisposing genes, which are well-known for increasing the risk of breast cancer in women, also increase the risk of MBC. In this regard, the significance of the *BRCA 2* gene mutation is much higher than that of its counterpart *BRCA 1* in causing male breast cancer [4, 8, 9]. Other genes associated with MBC with proven penetrance are *CHEK2*, *PALB2*, *TP53*, *PIK3CA*, and *RAD51* [10, 11]. A history of familial cancer was seen in 4–15% of cases [1].

Aging is one of the major non-modifiable risk factors, as MBC is thought to be a counterpart of breast cancer in post-menopausal females. Breast cancer in men occurs mostly in their 6^{th} to 7^{th} decades of life, with a more advanced disease stage; however, male breast cancer has been reported in patients aged from 5 to 93 years [1, 12–14].

The discrepancy in the estrogen-to-androgen ratio (and the conditions causing this) also has a high impact on the development of breast carcinoma in males. Klinefelter syndrome, one of such conditions, increases the risk of breast cancer by 50-fold and accounts for 3–7% of all MBC cases [7, 9]. Other factors that induce hormonal imbalance and result in MBC are obesity, liver and endocrine disorder, exogenous estrogen administration, and testicular abnormalities such as cryptorchidism, orchiectomy, or viral orchitis [14, 15].

Other risk factors with a high probability of causing MBC are occupational exposure to polycyclic hydrocarbon, long-term exposure to high temperature, and chest radiation due to other causes (these are supposed to suppress testicular function). Other rare risk factors are head trauma, marijuana and amphetamine abuse, which raises prolactin levels in the body, which is a risk factor for MBC [14]. A small number of cases of synchronous breast cancer and axillary tubercular lymphadenitis have been reported, particularly in tuberculosis-endemic countries [16]. The Association of MBC with neurofibromatosis is also documented in the literature although it is not clear whether it is a causative factor or a co-incidence [17]. However, some known risk factors for other cancer, such as smoking and alcohol intake, have not been demonstrated to contribute to developing breast cancer in men [18].

Histopathological classification

Infiltrating ductal carcinomas (IDC) account for more than 90% of cases of malignant lesions in male breasts [4]. Other less common varieties include lobular, papillary, secretory, and mucinous lesions (8–10%). The remaining carcinomas are rare tumors like sarcomas, lymphomas, and metastatic tumors from other primary cancers. The rarity of lobular carcinoma in males in comparison with females is due to the lack of terminal lobules in male breasts. Although rare, still infinitesimal cases of primary breast sarcoma are found in male breasts [19]. A few cases of basal cell and Merkel cell carcinoma of male breasts were also reported [20, 21]. Primary breast lymphoma, a relatively rare tumor, is also found in male breasts, but there is very little evidence [22]. Very rare cases of metastasis from other primary tumors spreading to male breasts have been described in the literature. Among these case reports, primary sites were the prostate, thyroid, cutaneous melanoma, urinary bladder, and kidney [23].

Clinical features

Most patients present in an advanced stage, either because of the lack of awareness, ignorance, low socioeconomic status, or taking indigenous treatment [1]. The NCI-SEER data reported that the incidence of stages at the time of presentation was 10%, 29%, 38%, 7%, and 8% for stages 0, I, II, III, and IV, respectively [15]. Most men (approx. 85%) present with complaints about a painless subareolar lump, which is hard, fixed, and unilateral in most cases [13, 14, 24]. Nipple involvement in terms of retraction, ulceration, and/or bleeding is present in 50% of cases [9]. Other common features include axillary mass, ulceration over the breast, and sometimes symptoms resulting from distant metastasis such as pain in bones, dyspnea, and abdominal pain. An old male patient having breast cancer presented with features of carcinoma *en cuirasse*, a rare form of cutaneous breast cancer metastasis [25].

Another rare presentation mentioned in the literature was pituitary symptoms in neuroendocrine tumors of male breasts [26]. Chances of distant metastasis in MBC are around 7–9% [15]. The most common site of distant metastasis is bone followed by the lung; others are the liver and brain. Isolated single-site metastasis is more common than oligo- or multiple sites involvement. Involvement of the left-sided breast in males is somehow more prevalent (L: R = 1.07:1) [15]; bi-laterality was seen in around 1% of cases [13, 27]. Unlike upper-outer quadrant involvement in females, MBC occurs predominantly in the central retro-areolar portion of the breast [27, 28].

Diagnostic workup

The approach to a patient with MBC is similar to that of a female patient. Earlier diagnosis could make a life-saving difference, as MBC is most often diagnosed in an advanced stage. Males presenting with suspected breast lesions should undergo a thorough clinical examination of both breasts and bilateral axilla, followed by using relevant imaging modalities such as ultrasonography, mammography, and magnetic resonance imaging (MRI), whenever needed [4]. Mammography is abnormal in nearly 90% of MBC and easily differentiates it from gynecomastia, the most common yet benign breast lesion in men [4]. Any lesion suggestive of malignant pathology should be confirmed by tru-cut biopsy; a biopsy is always preferable as the immunohistochemistry (IHC) assay leading to simultaneous hormone receptor status evaluation. HER2 (human epidermal growth factor receptor), a proto-oncogene, expression is estimated by IHC or fluorescent in situ hybridization (FISH). HER2-neu overexpression is associated with poor prognosis [7]. Genetic testing, particularly of BRCA and PALB2, is indicated in male breast cancer patients [11]. This testing helps not only in counseling the offspring or other family members but also to consider particular targeted therapies such as PARP inhibitors [11].

Staging is done according to the American Joint Committee on Cancer (AJCC) 8th edition of the TNM cancer staging system for female breast cancer [29]. Associated investigations to evaluate metastatic lesions, for treatment purposes and to supplement previous findings, are also done in the majority of the patients. Routinely, chest roentgenography, abdominal sonography, electrocardiography (ECG) and echocardiography, and blood investigations are done; special imaging techniques like MRI or computed tomography (CT) scans of the chest and/or abdomen, bone scintigraphy, and positron emission tomography (PET) scans are also used upon indications.

Prognostic factors

Male breast carcinoma has poor 5-year overall survival in the range of 40–65% in comparison to 80% in females [15]. But, when matched for age, stage, and hormone receptor status; female and male breast cancers revealed similar survival patterns. Other prognostic factors include tumor size, nodal status, stage, and hormone receptor status [13, 15].

Treatment strategy

Due to the few epidemiological data available in the literature, treatment guidelines for MBC are not standardized. Clinical practice generally follows

a copy-paste approach to their female version. However, timely diagnosis and early treatment strategy allow for the prevention of major complications. The treatment strategy, based on experience from female breast carcinoma, adopts a multimodality approach and consists of local therapy (surgery and radiation therapy), systemic therapy (chemotherapy, endocrine therapy, and targeted agents), and obviously, addressing metastatic lesions.

Surgery

Mastectomy has been the standard surgical approach in MBC. Despite the fact, that most treatment decisions about MBC including surgical interventions are extrapolated from the guidelines on female patients; breast conservative surgery (BCS) has not become popular in MBC. However, in some small-size trials, BCS was compared in terms of recurrence rate and survival [30]. The scarcity of male breast tissue may be the most probable cause of avoiding BCS in MBC. Other factors that encourage the surgeon to favor mastectomy are the central location of the tumor, nipple involvement, more advanced-stage disease at presentation, and regional nodal metastasis. Yet, the sentinel lymph node (SLN) biopsy technique was evaluated in some studies with a very good detection rate (90–100%) [9]. It can be concluded that the BCS and SLN biopsy techniques followed by axillary clearance in positive cases can be used in selected patients with good results. This limited surgical approach has the benefit of fewer long-term complications such as lymphedema and restricted shoulder movement. Farrow et al. [15] demonstrated positive outcomes of orchiectomy in metastatic MBC.

Radiotherapy

Radiation therapy (RT) is part and parcel of breast cancer management in females to prevent a locoregional recurrence. Similarly, postoperative radiation therapy is also incorporated into MBC management [4]. Indications and recommendations for adjuvant RT in MBC are the same as that for (female breast cancer) FBC. Moreover, RT is much more needed in MBC given the advanced stage of presentation. Conventional fractionation RT is most often evaluated in the literature on MBC treatment. The role of hypo- and ultra-hypo fractionation RT, which already turned out beneficial in FBC, is yet to be verified in MBC. In some advanced metastatic cases, palliative RT is also considered and, in that scenario, hypo fractionated dose schedules are preferred.

Post-mastectomy radiotherapy significantly improves disease-free (DFS) and overall survival (OS) irrespective of the stage, margin, and nodal status [1]. Yu et al. [5] demonstrated LRR improvement (without OS improvement) with PMRT in high-risk MBC cases such as patients with an advanced stage, node-positive, and ≤ 2 mm or unknown margin MBC [5]. The LRR rate without RT is approximately 5–20% in low-risk patients and 20–40% in high-risk patients. The LRR rate with PMRT is 8% and the 5-year local recurrence-free survival rate was 55–69% [1].

Chemotherapy

Chemotherapy drug and dose schedules for males with breast carcinoma are similar to those recommended in females; a few retrospective studies and case reports support these with documentation of better outcomes in adjuvant settings [1, 31, 32]. However, in a neoadjuvant setting, no case series or retrospective studies show any proper benefit which should be validated in future studies. In metastatic hormone-positive breast cancer, chemotherapy can be considered after at least two lines of endocrine-based therapy [33]. Furthermore, chemotherapy is a preferred option, particularly if there is a sign of imminent organ failure [33]. Drugs used in MBC in various studies are anthracylines, taxanes, cyclophosphamide, 5-fluorouracil, and, to some extent, platinum compounds, especially in metastatic disease. Initially, a CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil) was administered. The NCI MB-82 study showed that in nodal positive disease, 20-year survival is 42% after 12 cycles of CMF [34]. The MD Anderson Cancer Centre reported a reduced death risk with adriamycin-based chemotherapy [35]. Giordano et al. [35] reported 10-year OS with chemotherapy to be 43% in node-positive cases.

Endocrine therapy

Nearly 90% of men with breast cancer are found to be estrogen receptor (ER) positive, progesterone receptor (PR) positivity is also seen in around 95% of cases [9, 10, 36]. This high ER positivity and the role of hormonal imbalance in MBC causation define the significance of endocrine treatment as a cornerstone in MBC. MBC has been likened to post-menopausal FBC and so aromatase inhibitors (AI) should also be used as adjuvant treatment for MBC. However, most of the retrospective studies support the use of tamoxifen as the standard endocrine therapy in ER-positive male patients [7, 10, 31]. Although AIs were found to be effective in a few small case series, their use as first-line adjuvant hormonal treatment is not encouraged and is reserved for tamoxifen-failure cases and as dual hormonal therapy along with the GnRH agonist in metastatic breast cancer in males [32, 37]. The probable explanation for less guidance on AIs is their inability to prevent testicular estrogen synthesis, which corresponds to up to 20%

of endogenous estrogen in men. The current recommendation for adjuvant endocrine therapy in MBC is tamoxifen, and extended use of up to 10 years should be encouraged [38]. Notably, first-line hormonal therapy in metastatic MBC is again tamoxifen; and dual therapy, as mentioned earlier, is reserved for progressive cases [15].

Adverse effects of tamoxifen have been a topic of recent discussions. The side-effect profile of tamoxifen, obviously similar to that seen in female patients, is much more prominent in males. This causes poor compliance in male patients with breast carcinoma and affects treatment outcomes [39]. In fact, it shows that 10-year disease-free survival is more than double in compliant patients than in non-compliers. Poor compliance with tamoxifen in a lot of patients underscores the importance of alternative endocrine therapies. Options include luteinizing hormone-releasing hormone analogs, anabolic steroids, and bilateral orchiectomy in selected cases. These are even useful in metastatic hormone-positive breast cancers that progressed after tamoxifen therapy. However, sometimes tolerability of these drugs is poorer than tamoxifen despite their shown efficacy in different studies.

The role of neoadjuvant endocrine therapy in MBC has not been evaluated in any study to date; hence no recommendations are available. However, it can be a potentially useful strategy in selected patients due to the invariable hormone receptor-positive status of MBC. Hormonal therapy before surgery can shrink the tumor and may offer an opportunity for less extensive surgery. Moreover, short-term neoadjuvant hormonal therapy in receptor-positive patients can provide better patient compliance than long-term hormonal therapy, which has its own adverse effect. The recurrence rate is statistically significantly lower in patients who received both hormonal therapy and chemotherapy in comparison to chemotherapy alone [1].

Targeted agents

As mentioned earlier, the application of targeted agents in MBC is also based on observation of their benefits in FBC. However, given the rare HER2 positivity in MBC, the addition of trastuzumab (anti-HER2 agent) in a multimodality treatment approach to MBC is comparatively less frequent. Yet, in limited studies, benefits of adding trastuzumab, obviously in HER2-positive tumors and metastatic settings, turned out beneficial [40]. So, rational use of trastuzumab in HER2-positive metastatic breast cancer can be considered and more studies on this aspect are expected.

Among other targeted agents, the use of mTOR inhibitors (everolimus) and PARP inhibitors (olaparib) can be considered in MBC, provided these drugs have turned out to be efficacious in certain gene-positive FBC which are also found in MBC [11, 41]. Still, a lack of evidence and guidance for MBC has restricted their routine use by physicians. Another important class of drugs are CDK4/6 inhibitors such as abemaciclib and palbociclib. Benefits of these drugs in metastatic hormone-positive FBC were demonstrated in large randomized trials. Those famous trials also included a few male patients with breast cancer, and those patients were also found to have benefited from the treatment. So, it can be concluded that the use of these CDK4/6 inhibitors is preferred as 1st-line therapy in metastatic hormone-positive breast cancer – not after endocrine therapy or chemotherapy [41].

Indian setting of MBC

In India, the incidence rate of MBC was reported to be 0.4%, 0.5%, and 4.1% of all breast cancer cases as reported by Chikaraddi et al., Rai et al., and Shah et al., respectively [42–44] . A few retrospective studies on MBC have been reported from India (Tab. 2 [1, 12, 15, 19, 28, 42–48]). These studies are important to understand the current situation of MBC in different parts of India. Some other rare case presentations on MBC were also reported in the literature from India (Tab. 3 [3, 4, 9, 13, 24, 27, 32, 36, 49–51]).

These retrospective studies depict approximately similar presentations and course of the disease. In the majority of the studies, more than 80% of patients had IDC and most were hormone receptor positive [15]. The MBC cases constituted from 1.03% to 2.5% of total breast cancer patients [12, 45]. The median age at diagnosis was from 54.2 to 67 years (Tab. 2). Half of the studies reported the median age as 55 years, which is somewhat less than the age that is reported in the literature [12]. The other half had a median age of around 62 years (Tab. 2). Surprisingly, the involvement of the right breast is more frequent (74%) [12]. Most of the patients presented in an advanced stage (III or IV) and many of them underwent mastectomy [15, 45]. The late presentation was caused by the lack of awareness, ignorance, low socioeconomic status, or taking indigenous treatment [1].

Most patients (60%) presented with distant metastasis, mostly bone involvement alone or in combination with visceral metastasis. All the patients had good general condition despite having metastatic disease; non-metastatic patients underwent primary surgical intervention [45]. Adjuvant chemo- and radiation therapy was given according to indications, and tamoxifen was administered for all hormone-positive patients [15, 45].

In a retrospective study on primary breast sarcoma by Ahuja et al. [52], 3 of 5 patients with breast sarcoma were male, which constituted 0.2% of all

Table 2. Summary of case series/research reports on male breast cancer in India

Study	Shukla et al. [19]	Rai et al. [43]	Mitra et al. [46]	Shah et al. [44]	Chikaraddi et al. [42]	Shah et al. [15]	Mukherjee et al. [47]	Sundriyal et al [45]	Gogia et al. [48]	Ram et al [28]	Pothamsetty et al. [12]	Yadav et al. [1]
Year	1996	2005	2007	2009	2012	2012	2014	2015	2015	2017	2017	2018
No. of patient	41	30	79	32	26	42	33	18	27	27	23	81
Median age [years]	54.2	56	67	55	57	56	60	60	62.6	62.6	56	57
Early disease	–	–	–	–	–	40%	–	11%	59%	85%	–	37%
Locally advanced disease	41%	43.3%	90% (stages 3 and 4	56.2%	50%	43%	57.6%	28%	–	15%	87%	42%
Metastatic disease	–	–	–	–	–	17%	–	61%	–	–	22%	21%
Mastectomy	–	–	–	–	–	86%	–	39%	–	100%	–	86%
Node positive	–	–	–	–	–	60%	–	28%	–	33%	–	59%
ER/PR +ve	43%	–	83%	62.5%	81%	27%/62%	54.5%	89%	78%	78%	56.5%	42%/26.5%
HER 2 +ve	–	–	–	–	–	–	–	11%	–	7.4%	4%	3%
PMRT	–	–	–	–	–	67%	–	–	–	22.2%	–	80%
Chemo	–	–	–	–	–	67%	–	–	–	70.4%	–	55%
Tamoxifen	–	–	–	–	–	90%	–	–	–	77.8%	–	70%
Median follow-up [months]	–	–	–	–	–	17 months to 136 months	–	–	–	–	24	60
LRR	–	–	–	–	–	14%	–	–	–	–	4%	12.5%
Distant metastasis	–	–	–	–	–	12.5%	–	–	–	–	22%	34%
DFS	–	40% (5 yr)	47–78% (5 yr)	–	–	46% (5 yrs)	–	–	–	76.3% (5 yr)	43%	42% (10 yrs)
OS	91.4% (4 yr)	–	–	–	–	–	–	–	80% (3 yr)	92.3% (5 yr)	74%	53% (10 yrs)

DFS — disease-free survival; ER/PR — estrogen receptor/progesterone receptor; HER — human epidermal growth factor receptor; LRR — loco-regional recurrence; OS — overall survival; PMRT — post-mastectomy radiotherapy

Table 3. Summary of case reports on male breast cancer in India

Study	Age	Laterality	Surgery	No of positive LN	Stage	HR status	HER2 status	CT given	HT given	RT given	Metastasis
Sarma et al. (2013) [36]	58	Right	Yes	1	IIA	ER + ve PR + ve	NK	Yes	Yes (T)	No	Nil; synchronous base of tongue cancer
Hariprasad et al. (2013) [24]	50	Left	Yes	Nil	II	ER + ve PR + ve	NK	No	No	No	Nil
Jagtap et al. (2014) [13]	70	Bilateral	Yes	2/10 (L) 0 (R)	IIIB (L) IIA (R)	ER + ve PR + ve	-ve	Yes	NK	NK	Nil
Gupta et al. (2015) [3]	73	Right	Yes	Nil	IIB	ER + ve PR + ve	equivocal	No	Yes	Yes	Nil
Agrawal et al. (2015) [49]	65	Right	Yes	5/16	IIB	ER + ve PR +ve	-ve	Yes	Yes (T, AI)	Yes	Multiple
Samanta et al. (2015) [50]	60	Right (chest wall)	No	NA	NA	ER + ve PR + ve	-ve	Yes	No	No	Nil; Ectopic breast cancer in the right chest wall
Uthamalingam et al. (2016) [32]	51	Left	Yes	1	IIIB	NK	NK	No	No	No	Nil; Paget's disease of the ipsilateral nipple
Mishra et al. (2018) [9]	62	Left	Yes	Multiple	recurrent	ER + ve PR + ve	-ve	Yes	Yes (T)	Yes	Multiple
Garg et al. (2018) [51]	64	Left	Yes	2	IIIB	ER + ve PR + ve	NK	Yes	Yes	Yes	Nil; synchronous basal cell carcinoma of left eyelid
Hazarika et al. (2019) [4]	63	Left	Yes	Multiple	IIIA	ER + ve PR + ve	NK	Yes	Yes (T)	Yes	NK
Kadam et al. (2020) [27]	60	Bilateral	Yes	Nil	IIA (R) IIB (L)	ER + ve PR + ve	-ve	Yes	Yes (T)	Yes	Nil

AI — aromatase inhibitor; CT — chemotherapy; ER — estrogen receptor; HER — human epidermal growth factor receptor; HR — hormonal receptor; HT — hormonal therapy; L — left; LN — lymph node; NK — not known; PR — progesterone receptor; R — right; RT — radiotherapy; T — tamoxifen;

breast malignancies. The 3 male patients had either leiomyosarcoma, dermatofibrosarcoma protuberans, or malignant peripheral nerve sheath tumors [46]. Various other studies summarized in Tables 2 and 3, which were retrospective in nature, demonstrated that patients' age at diagnosis was the 6th to 7th decade, they presented in a locally advanced stage, more than three-fourths were hormonal receptor-positive, and surgery and radiation were the mainstay of treatment and prognosis, which is a somewhat lower value than that in the case of female counterparts.

Limitations of those studies are small sample size, retrospective nature, and single-center experience. It can be recommended that male BC patients should be routinely included in all breast cancer trials unless there is a strong biological reason to exclude them. This will help researchers to achieve a better systematic characterization of MBC patients, including genetic mutations and tumor subtypes.

Conclusions

Breast cancer in males is still an unaddressed issue, especially in countries like ours where the doctor-to-patient ratio is very low and there are relatively few cancer awareness programs. More knowledge regarding such a life-threatening condition, in both doctors as well as the general population, would surely help in early diagnosis, proper treatment, and distant-site metastasis prevention. The importance of awareness of breast cancer in men should be highlighted, as lack of knowledge

contributes to delayed diagnoses established in advanced stages. The role of adjuvant systemic therapy deserves more research as well.

Author contributions

A.S.: conceptualization, methodology, formal analysis, original manuscript writing; D.P.: conceptualization, review of literature, original manuscript writing; P.K.: review of literature, final manuscript editing; A.C.: supervision, final manuscript editing; V.K.: supervision, final manuscript editing; M.V.: software, review of literature.

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Conflict of interest

Authors declare no conflict of interest.

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REVIEW ARTICLE

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Spermatic cord tumors — review of the literature

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ABSTRACT

In this article, we discuss benign and malignant spermatic cord tumors.

We attempted to compile this rare group of diseases by reviewing the international literature.

Tumors of the spermatic cord are found very rarely. However, it is important to be aware of their occurrence, as they can cause a protrusion in the inguinal area. They are usually misdiagnosed as an inguinal hernia.

The most common tumors in this area are benign — usually they are lipomas. In 20–70% of cases, adipose tumors accompany an inguinal hernia. Therefore, they should be kept in mind whenever a patient presents with symptoms of herniation in the inguinal region. Tumors of the spermatic cord may also involve the scrotum and manifest themselves as testicular hydrocele. Such a tumor is, for example, aggressive angiomyxoma. It is a locally malignant tumor that tends to infiltrate and compress the surrounding tissues but does not tend to give metastasis, therefore according to the WHO classification it is a benign tumor.

However, malignant tumors such as rhabdomyosarcoma, which is the most common malignant neoplasm of testicular appendages, can also be located in the spermatic cord. The second most common soft tissue sarcoma is leiomyosarcoma, with poor initial prognosis, or metastases of malignant tumors from other organs, e.g. renal adenocarcinoma.

As the prognosis for malignant tumors of the spermatic cord is generally dependent on the stage at the time of diagnosis, oncological vigilance and early diagnosis allow for faster detection of these tumors, which may improve the prognosis of patients with tumors in this location.

Key words: benign tumors, malignant tumors, tumor, spermatic cord, vas deferens

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Introduction

Tumors of the spermatic cord are a rare heterogeneous group of diseases. They are usually benign lesions. However, in the minority of cases, malignant neoplasms and metastases of the neoplastic process from another location, such as metastases of renal adenocarcinoma, may also occur within the spermatic cord [1].

Non-malignant tumors of the spermatic cord include lipoma, leiomyoma, rhabdomyoma, cellular angiofibroma, haemangioma, and aggressive angiomyxoma [2].

Malignant tumors of the spermatic cord are very rarely described in the literature.

Malignant lesions originating from adipose tissue and involving the spermatic cord are well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma. A very rare tumor of the spermatic cord originating from smooth muscle tissue that can also spread to the spermatic cord is leiomyosarcoma [2, 3].

The spermatic cord may also be affected by tumors such as rhabdomyosarcoma, desmoplastic small round cell tumor, and metastatic tumors [2, 3].

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Benign tumors of the spermatic cord

Lipoma

Lipomas of the spermatic cord are the most common benign tumors in the inguinal canal [4–6]. The incidence of spermatic cord lipoma (without a hernia sac) is 1–8% [7]. A spermatic cord lipoma usually accompanies an inguinal hernia (20–70% of cases with or without a hernia sac) [8–10]. These tumors may increase the size of the inguinal hernia and be misdiagnosed as just an inguinal hernia [8–10]. They are often diagnosed during hernioplasty [8]. A spermatic cord lipoma is usually located deep in the testicular levator muscle and fascia [6].

This tumor is a pre-peritoneal adipose tissue that shows communication with the spermatic cord. This fat merges with the fatty layer within the internal seminal fascia [11, 12]. This is not a true lipoma, which is a benign tumor of adipocytes confined to the inguinal canal and showing no connection to the retroperitoneal fat [11]. However, the term "lipoma spermatic cord" has become entrenched in clinical terminology and is still used. The term "true" adiposity can only be applied to adipomas that are confined to the inguinal canal and show no continuity with pre- or retroperitoneal fat [4–6].

Spermatic cord lipomas usually cause typical symptoms like an inguinal hernia i.e. bulging and pain, so it is recommended that they be treated in the same way as an inguinal hernia [8, 13]. They should also always be clinically suspected when patients report groin pain in the absence of a bulge in the inguinal region [8].

Ultrasonography (USG) is usually able to detect spermatic cord lipoma. A lipoma on ultrasound is visible as a hyperechoic mass [14]. In doubtful situations, computed tomography (CT) or magnetic resonance imaging (MRI) are recommended [15, 16].

Leiomyoma

Leiomyoma is a benign smooth muscle tumor. This tumor can occur in almost any organ but is most commonly described in the uterus [17, 18].

A review of the literature has so far described single cases of leiomyoma in the genitourinary system — usually in the bladder, epididymis, prostate, testis, and penis [19–24]. Leiomyoma of the spermatic cord is very rare. Since 1949, only three cases of this tumor in the spermatic cord have been described in the literature.

Based on the cases described, it usually manifests as a protrusion mimicking an inguinal hernia with or without scrotal involvement [25]. The authors of these articles recommend that the treatment of leiomyomas should be individual, but once the lesion has been resected, treatment such as that of an inguinal hernia is recommended [25].

Rhabdomyoma

A rhabdomyoma is a benign tumor that accounts for only 2% of all tumors arising from striated muscle [1]. This tumor very rarely affects the spermatic cord. To date, two cases of rhabdomyoma of the spermatic cord have been described [26, 27]. One of these cases was a 67-year-old man with an adult-type subtype. In this patient, the tumor originated from the testicular levator muscle. Seven years later, a case study on a 28-year-old man with rhabdomyoma of the spermatic cord was published [27], and so far no further cases have been described.

In general, rhabdomyomas are slowly growing tumors with a low tendency to recur after radical excision [26].

Cellular angiofibroma

Cellular angiofibroma in men can occur in the spermatic cord (vas deferens) but can also involve the epididymis, the vaginal sheath, and the inguinal region and scrotum [28]. It is a benign mesenchymal tumor that lacks differentiation into smooth muscle, nerves, epithelium, and myoepithelium [29, 30].

It is usually characterized by a benign course with slow growth and no tendency to metastasize [31]. However, this tumor may recur. It is often misdiagnosed as an inguinal hernia [32].

For the treatment of cellular angiofibroma of the spermatic cord and if the tumor involves other perinuclear structures during resection of the lesion, testis-sparing methods are recommended [32].

Hemangioma

Hemangioma is a very rare benign tumor of the spermatic cord. It is characterized by slow growth. [33]. This tumor is usually localized in the inguinal region and scrotum [34]. Since 2009, several cases of anastomosing hemangioma of the spermatic cord have been described [35]. This is a rare subtype of spermatic cord hemangioma. Usually, this tumor is localized in the kidney [36–38]. It is a tumor that is characterized by a benign course [35, 39, 40], but it tends to recur. Nevertheless, isolated cases of anastomosing hemangioma and metastasis have been described in the literature. This tumor presents diagnostic difficulties as it shares many features with malignant sarcomas [41].

Symptoms of spermatic cord hemangioma are usually pain at the tumor site, a palpable protrusion, and sometimes hematuria is also found. On ultrasound diagnosis, anastomosing hemangioma is usually a hypoechoic or anechoic cystic lesion [36, 37]. It may also show increased marginal ascularization with the use of Doppler techniques [38]. In contrast, on CT anastomo-

sing hemangioma is seen as a hyperdense lesion with hypodense structures visible in the central part. The lesion on CT may undergo peripheral enhancement after a shadowing agent administration [39]. On MRI, anastomosing hemangiomas tend to be hypointense on T1WI and hyperintense on T2WI and DWI. Additionally, the tumor may undergo peripheral shadowing agent enhancement in the arterial phase and show central component enhancement in the venous phase [42].

Surgical resection of the tumor is recommended for the treatment of urogenital anastomosing hemangioma. In doubtful cases, some authors recommend orchidectomy. In contrast, other authors recommend a biopsy of the lesion before performing a radical resection with or without orchidectomy. However, this examination can be challenging, especially when the tumor shows a heterogeneous histological structure [43].

Aggressive angiomyxoma

It is a locally aggressive tumour characterised by slow growth. Histologically, it is benign in nature. The local malignancy of this lesion is that the tumour can infiltrate and compress the surrounding tissues. It shows a tendency to recur and expresses to hormone receptors. The literature reports that this tumor does not metastasize [44, 45]. Eight cases of the localization of this tumor in the spermatic cord have been described to date in the international literature [44, 45]. This tumor usually presents with enlargement of one-half of the scrotum on the tumor side. It may also imitate a testicular hydrocele. Intraoperatively, a gelatinous mass is found adjacent to the testis, extending into the spermatic cord. Treatment recommends resection of the lesion with testicular sparing [44].

Malignant tumors of the spermatic cord

Liposarcoma

Liposarcoma is the most common soft tissue sarcoma. This tumor accounts for 9.8–18% of soft tissue sarcomas. The peak incidence of this tumor is between 40 and 60 years of age. The incidence of this tumor in the scrotum is 3.6%, while in the spermatic cord, the tumor is located with a frequency of 76%. Other locations include the testicular membrane (20%) and epididymis (4%) [46].

According to the World Health Organisation (WHO) classification [2], there are several subtypes of adenosarcoma: well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma.

A symptom of liposarcoma may be a painless tumor of the inguinal or scrotal region. On physical examination, a hard, non-painful tumor is palpable [46]. A well-differentiated liposarcoma requires confirmation of MDM2 amplification during diagnosis [47]. De-differentiated liposarcoma and well-differentiated liposarcoma share amplifications in the chromosomal region 12q13-15. These amplifications involve MDM2 (100%) and often CDK4 (90%).These amplifications can be detected by fluorescence in situ hybridization (FISH), which is now recognized as the standard for differential diagnosis [48, 49]. However, FISH requires specific equipment that is only available in specialized centers. Therefore, immunohistochemistry (IHC) can be used as an easier method in application and availability [50].

In general, the treatment of liposarcoma depends on the stage of the tumor and histological type. As is well known, soft tissue sarcomas have a high tendency to recur even after previous resection [3]. Generally, surgical resection of the tumor is the primary method of treatment, but this is not always possible and sometimes, even if performed, is insufficient due to local recurrence [51]. Usually, the efficacy of adjuvant chemotherapy (CTH) and radiotherapy (RTH) is low. Single reports have described recurrences more than 10 years after tumor resection, so long-term careful follow-up of the patient after treatment is required [46].

The prognosis In liposarcoma for all sites is dependent on tumor histology. Well-differentiated liposarcoma and myxoid liposarcoma have a better prognosis than other histological subtypes of this tumor.

According to the literature, 5-year survival in well-differentiated liposarcoma is approximately 85%, in the myxoid subtype it is 77% and in other subtypes of this tumor, it is 20% [52].

However, liposarcomas can undergo differentiation. They may most commonly differentiate approximately 7.7 years after the diagnosis of the well-differentiated type. When a liposarcoma differentiates, 5-year survival drops to 28%. Differentiation occurs most commonly in recurrent tumor metastases [53, 54].

Leiomyosarcoma

Leiomyosarcoma of the spermatic cord is a rare malignant tumor of this region. However, a review of the literature suggests that 75% of soft tissue sarcomas in men originate from the spermatic cord [5]. Usually, leiomyosarcoma of the spermatic cord originates from its distal segment.

Leiomyosarcoma of the spermatic cord may imitate an incarcerated inguinal hernia. In addition, it can be confused with an epididymal cyst, a lipoma spermatic cord, and epididymo-orchitis. The clinical presentation of this neoplasm is usually vague and atypical. The patient may report the presence of a palpable

painless mass in the groin and scrotal region [55]. The peak incidence is between 50 and 60 years of age [56]. Leiomyosarcoma of the spermatic cord is the second most common soft tissue sarcoma.

To date, 113 cases of leiomyosarcoma of the spermatic cord have been described worldwide [57].

The neoplasm spreads in three ways, through local-regional, hematogenous, and lymphatic routes. Local spread is the most common. Hematogenous spread generally involves the liver and lungs while lymphatic spread involves the external iliac, subcostal, paraaortic and common iliac nodes [58].

Ultrasound and CT are helpful in the diagnosis, but the final diagnosis is based on histopathology and immunohistochemistry [55].

Due to its rarity, there is no official position on how to treat this tumor [56]. Orchidectomy with excision of the spermatic cord up to the deep inguinal ring is recommended when the tumor is resectable [57]. Local recurrence is estimated to occur in 30–50% of cases [59]. In the literature, recurrence of this tumor has been described even 15 years after the initial diagnosis [60].

There is also no official position as to the use of RTH. Some authors advocate the use of adjuvant radiotherapy after orchidectomy to reduce local recurrence [61].

Chemotherapy is often used when metastases are present [56]. In contrast, lymphadenectomy of the surrounding lymph nodes is only recommended if they are enlarged. The overall prognosis in leiomyosarcoma, at any location, is poor.

Rhabdomyosarcoma

Rhabdomyosarcoma is a rare malignant tumor that can also occur in the spermatic cord. To date, 62 cases of this neoplasm in the spermatic cord have been described [62, 63]. Rhabdomyosarcoma is the most common malignant neoplasm of the testicular appendages in patients aged 7 to 36 years, and its peak incidence is in the first two decades of life [64, 65].

The WHO classification of tumors of the spermatic cord and testicular appendages distinguishes four subtypes of rhabdomyosarcoma [2]: embryonal type, alveolar type, spindle cell type, and pleomorphic type.

Embryonal type

The embryonal type of rhabdomyosarcoma is the most common subtype of this tumor in children and young adults [63].

Pleomorphic type

In adults, it is most commonly localized in the deep tissues of the extremities [3].

Alveolar type

In this type of rhabdomyosarcoma, chromosomal translocations are most commonly found. The usual translocation found is t(2;13) (q35;q14) with the formation of a fusion between the *PAX3* gene on chromosome 2 and the *FKHR* gene found on chromosome 13. Another translocation found is t(1;13) (p36;q14).

PAX3 acts as a cascade gene for other genes controlling differentiation into skeletal muscle. Tumor development most likely occurs as a result of disruption of the muscle differentiation process by a chimeric protein formed after PAX3-FKHR fusion [66, 67].

Spindle cell type

In children, it is most commonly localized within the scrotal sac [68].

Rhabdomyosarcoma usually manifests as a painless palpable tumor in the epididymal region or as an enlargement of the scrotum on the tumor side [63]. In addition, enlarged inguinal lymph nodes are often found on physical examination also on the side of the lesion.

In the treatment of rhabdomyosarcoma of the spermatic cord, there are no strict management guidelines due to the rarity of this tumor. Most authors advocate the need for orchidectomy regardless of tumor stage. Lymph node metastases may affect up to 50% of patients with this tumor, so lymphadenectomy of the involved retroperitoneal lymph nodes is recommended. Depending on the stage of the tumor and the presence of metastases, adjuvant CTH is necessary for some patients [69, 70].

The unfavorable prognosis for survival increases from embryonal to pleomorphic to follicular forms. The prognosis in rhabdomyosarcoma depends on its stage. This neoplasm is curable in almost two-thirds of cases in the pediatric population. In contrast, pleomorphic forms in adults have a significantly worse prognosis. The spindle cell type in adults is characterized by an aggressive course [66–68].

Desmoplastic small round cell tumor

This is a tumor characterized by high malignancy and high grade already at the time of diagnosis. One of the few cases of a patient being cured of this tumor has been reported in the literature [71]. In the cited case of a 14-year-old boy, the tumor imitated an inguinal hernia. In the patient, the testis was not occupied by the tumor. The patient received 17 cycles of adjuvant CTH with vincristine, topotecan, cyclophosphamide, doxorubicin, etoposide, and ifosfamide after surgical treatment. In addition, the boy received 50.4 Gray of adjuvant irradiation to the tumor bed after the sixth cycle of chemotherapy. The boy was treated for 3 years and 1 month and remained on active oncological follow-up with no signs of local recurrence or distant

metastases. In that case, it was not specified whether the lesion had infiltrated the spermatic cord. However, it was a tumor of the perinuclear structures, which must be considered in the differential diagnosis of spermatic cord tumors [71].

Due to the rarity of this tumor, there are no established management guidelines. In our review of the literature, the preferred method of management for tumors in the inguinal region is to perform tumor resection, often with orchidectomy from inguinal access, with high resection of the spermatic cord. The standard of care for this tumor is neo- or adjuvant multidrug CTH (regimens are similar to those for Ewin sarcoma). On the other hand, RTH is proposed for patients who cannot undergo surgical resection [72].

Overall, 5-year survival in this tumor (for any location) is low at 15–20% [72]. Patients with a tumor location in the inguinal region have a better prognosis than patients with other tumor locations. This is because the tumor is more easily accessible, which increases its detectability. Patients can more easily palpate the lesion on self-examination and see a urologist more quickly.

In this group of patients, quoting from the authors of the cited article, 60% of patients were alive up to 120 months after treatment [71, 72].

Metastatic tumors

Metastasis of tumors from another location to the spermatic cord is extremely rare.

Usually, the prognosis for patients with metastases to the spermatic cord is poor due to the mere presence of metastatic disease [73]. The primary tumor usually occurs in the gastrointestinal tract [73]. Metastases to the spermatic cord of tumors such as renal adenocarcinoma [1] and pancreatic adenocarcinoma [74, 75] have also been described in the literature. Treatment includes inguinal orchidectomy with high spermatic cord resection and postoperative chemoradiotherapy [75].

Conclusions

Tumors of the spermatic cord are generally benign. The most common benign tumor in this area is lipoma. However, the incidence of malignant tumors of the spermatic cord can be as high as 30% [76]. It is also worth noting that approximately 46% of soft tissue sarcomas are located in the thigh, buttock, and inguinal regions [77]. Therefore, it is recommended that careful differential diagnosis of tumors of the groin area should be performed, and that most lesions of this area should not be treated as inguinal hernia.

Author contributions

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Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Strikingly high activity of metronomic chemotherapy in a patient with locally advanced, life-threatening cutaneous squamous-cell cancer — case report and discussion of the literature

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ABSTRACT

The current treatment of choice in patients with advanced or metastatic squamous-cell carcinoma (SCC) of the skin is immunotherapy based on anti-PD1/L1 antibodies. For many years, there has been a consensus, that SCC of the skin is a chemorefractory neoplasm. However, despite a recent approval of checkpoint inhibitors for the treatment of cutaneous SCC, their extremely high cost makes them unavailable for many patients worldwide, and additionally, in many patients, their use may be contraindicated by patients' clinical conditions. This article provides strong arguments that optimized and well-matched chemotherapy still represents an active treatment option even in the era of novel therapies.

Key words: metronomic chemotherapy, skin squamous-cell carcinoma, skin cancer, cutaneous malignancies

Oncol Clin Pract 2023; 18, 3: 174–177

Introduction

Squamous-cell carcinoma (SCC) of the skin, originating in keratinocytes, is the second most common, non-melanocytic cutaneous malignancy after basal-cell carcinoma. The primary treatment modality in a locoregional disease is a wide resection with optional adjuvant radiotherapy. In the case of locally advanced or disseminated disease, the current systemic treatment is immunotherapy based on anti-PD-1/L1 antibodies [1, 2]. The very high costs of checkpoint inhibitors make these drugs unavailable for many patients worldwide. Still, even when immunotherapy is available, its use may be inappropriate in many cases of advanced, symptomatic SCC patients due to the risk of a rapid, immediately life-threatening progression of tumor lesions. The current article presents a clinical case of a patient with severely symptomatic, locally advanced skin SCC in whom immunotherapy was contraindicated and who experienced a complete response with multidrug metronomic chemotherapy. This article provides strong arguments that optimized and well-matched chemotherapy still represents a promising treatment option even in the era of novel therapies.

Case report

A 75-year-old patient with a massively advanced SCC of the skin penetrating deeply in the direction of the spinal bulb (Fig. 1A) was admitted to the Oncology Department of the University Hospital in Krakow

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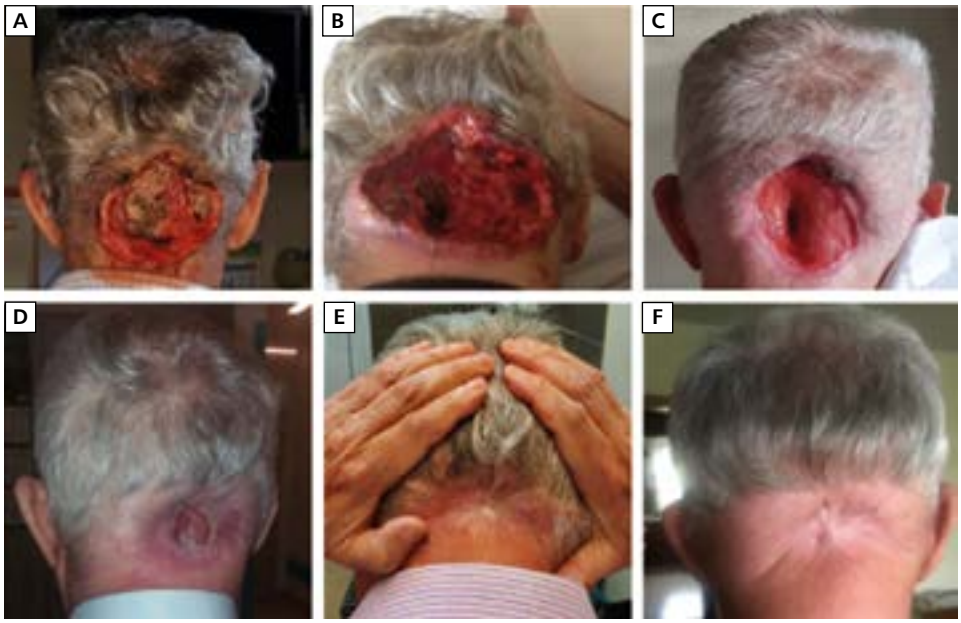

Figure 1. Stages of response of locally advanced squamous-cell carcinoma of the skin to metronomic chemotherapy; **A.** Before initiation; **B.** Progression during MCC (Methotrexate, Cyclophosphamide, Capecitabine) regimen; **C.** One month after initiation of oral metronomic chemotherapy (CPC) regimen; **D.** At the time of initiation of de-escalated CPC-based chemotherapy; **E.** Complete clinical response at the time of initiation of consolidative radiotherapy; **F.** Six months after consolidative radiotherapy

in August 2019. The diagnosis was established 2 months earlier, but due to the patient's condition and the size and location of the lesion, he was not qualified for a local and systemic treatment. There were objective contraindications for immunotherapy because of the risk that a paradoxical progression might result in life-threatening spine compression. Chemotherapy was not offered because of the patient's poor performance status [Eastern Cooperative Oncology Group (ECOG) = 2] and bleeding risk.

Magnetic resonance imaging (MRI) performed one month before admission revealed massive infiltration of the skin and subcutaneous tissues of the occipital and neck regions penetrating the intermuscular fascia (Fig. 2A–B). Before initiation of treatment, the patient complained of severe pain radiating to the head and neck. The ulcerated crater-like lesion in the skin, 8 cm in diameter, penetrated deeply into subcutaneous tissues and was filled with necrotic, inflammatory masses that bled intensively upon contact (Fig. 1B). The patient's relatively poor condition and severe symptoms (inability to remain in a lying position) did not allow for performing baseline computed tomography (CT) or MRI. Ultrasound examination of the abdomen and chest radiography revealed no signs of dissemination. Additional pathomorphological verification showed no estrogen, progesterone, or androgen receptor expression and a low proliferation rate (Ki67 = 9.5%). Considering the patient's symptoms, performance status, and an imminent threat to his life in case of further disease progression,

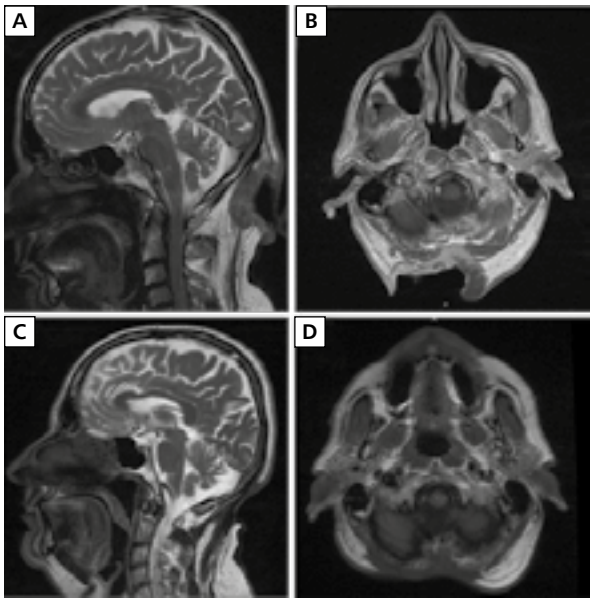

Figure 2. Magnetic resonance scans of the head and neck region; **A, B.** Before initiation of metronomic chemotherapy; **C, D.** At the end of chemotherapy

he was started on metronomic chemotherapy based on an all-oral MCC (Methotrexate, Cyclophosphamide, Capecitabine) — Methotrexate 5 mg per os (p.o.), administered twice a week, Cyclophosphamide 50 mg p.o. q1d, and Capecitabine 500 mg p.o. tid.

Four weeks later, further, however subjectively less dynamic, clinical progression occurred. The patient complained of increasing pain, weight loss, and neurological symptoms of paresthesia in the lower and upper limbs. The paresthesia most likely resulted from the penetration neoplastic of the lesion into the cerebellum and spinal bulb (Fig. 2B). Therefore, an intensified intravenous/oral metronomic chemotherapy (CPC) regimen was initiated. In October 2019, the patient started on cisplatin 25 mg/m^2 intravenous (i.v.) and paclitaxel 50 mg/m^2 *i.v.* (administered on days 1, 8, and 15, repeated every 28 days) in combination with capecitabine (500 mg p.o. tid).

Within the next 2 weeks, the modified metronomic treatment resulted in a clinically significant reduction of pain and a gradual decrease in the lesion diameter. After 1 month of treatment with the CPC regimen, signs of response were observed (Fig. 1C). Initially, chemotherapy was associated with increased bleeding from the wound, but after 1 month, the bleeding subsided. Relief in pain and neurological symptoms was also observed. The patient discontinued opioids before the end of the second month of the CPC treatment. After 7 months of intensive (weekly) chemotherapy, when a major response was determined, the patient requested longer treatment intervals due to personal reasons. He continued to receive intravenous chemotherapy at 2-weekly intervals (at initial doses) and capecitabine daily (500 mg p.o. tid). Since then, the lesion has remained clinically stable (Fig. 1D). Magnetic resonance imaging done in August 2020 showed complete regression of the neoplastic lesion (Fig. 2C–D). Chemotherapy was administered for 15 months until a clinical complete response was confirmed (Fig. 1E). Considering the treatment benefit and emerging signs of ototoxicity (Grade 1 hearing loss from January 2021), systemic treatment was stopped entirely, and the patient was scheduled for consolidation radiotherapy, and currently, 6 months later, remains in observation and in complete remission (Fig. 1F). The long-term treatment with multidrug metronomic chemotherapy was tolerated very well. The administration of chemotherapy had to be postponed only twice due to Grade 2 neutropenia.

Discussion

Locally advanced or disseminated SCC of the skin is rare. The scarce data regarding the efficacy of classical systemic therapies in these clinical conditions come from small and retrospective studies or case series reports. The primary cytotoxic agents used to treat skin SCC are platinum compounds (mainly cisplatin), and additional drugs are taxoids, fluoropyrimidines, or bleomycin used alone or in combination. Recently, immune checkpoint inhibitors (cemiplimab and pembrolizumab) have been approved for the treatment of patients with advanced/metastatic skin SCC [1, 2]. In a pivotal phase I/II clinical study conducted in advanced/metastatic skin SCC patients, administration of cemiplimab was associated with a high rate of long-lasting objective responses (approximately 50%) [1]. However, complete responses (7%) occurred only in metastatic SCC patients, and 12–19% of patients failed to respond. Additionally, approximately 20% of patients progressed despite the initial benefit from immunotherapy. Another drug, pembrolizumab, which achieved 34% of objective responses (4% complete responses) was inactive in more than 26% of patients with skin SCC.[2] While considering immunotherapy, physicians must remember that despite its significant activity, many patients with advanced, symptomatic, or locally advanced tumors may not benefit from this therapy and experience early progression (sometimes even hyperprogression). In our patient, due to the highly symptomatic disease and life-threatening clinical conditions, the use of immunotherapy was contraindicated, and the only treatment option that remained was chemotherapy.

The activity of chemotherapy in SCC of the skin is modest at best. In a retrospective analysis of 19 patients (13 with locally advanced and 6 with metastatic SCC), monotherapy (paclitaxel, cisplatin, or carboplatin) led to 44% of objective responses while multidrug cisplatin-based regimens to up to 53% [3]. Median progression-free survival (PFS) was 5.5 months and median overall survival (OS) was 10.9 months. Still, no significant differences in PFS and OS were found between patients receiving single- or multidrug regimens. Another study evaluated combined chemotherapy (cisplatin, fluorouracil, and bleomycin) in 13 patients with locally-advanced SCC of the skin [4]. Such aggressive multidrug chemotherapy led to 30% of complete responses at the cost of substantial toxicity in more than 40% of patients. Another highly toxic chemotherapy regimen [weekly multi-agent chemotherapy CMF-b (Cyclophosphamide, Methotrexate, Fluorouracil, Bleomycin)] was evaluated in 26 patients with surgery-ineligible SCC and basal-cell carcinomas of the skin [5]. The treatment was associated with objective responses in 61.5% of patients, with 27% of complete and 34% of partial responses, but the median duration of response was only 6.1 months.

The available data on systemic therapies of advanced/metastatic SCC of the skin, albeit of low quality, demonstrate that treating symptomatic, usually elderly, patients represents a considerable challenge. Immunotherapy with checkpoint inhibitors is currently the treatment of choice in advanced/metastatic SCC of the skin. Still, its use may be significantly restricted in

patients with severe symptoms or a high disease burden. Additionally, due to their cost and reimbursement issues, the availability of immunotherapies represents another socially significant problem.

Metronomic chemotherapy is a reasonable therapeutic approach in many patients with advanced, non-rapidly proliferating cancers, especially those who are elderly or have significant comorbidities [6–12]. The oral-intravenous approach presented in this article represents smart combined chemotherapy designed to activate all possible mechanisms of the cytotoxic drugs used. These mechanisms engage not only the standard antiproliferative activity of cytotoxic agents but also their antiangiogenic and immunostimulatory potential induced by continuous low-dose administration. Those targeted therapeutic properties of metronomic chemotherapy are considered an alternative in many low-income countries with restricted access to targeted agents. However, as shown in our patient's case, this approach may still represent a treatment of choice even if some novel advanced therapies are available. Based on the literature and the presented case report, there is no doubt that a skillful adjustment of chemotherapy to biological properties of particular tumors allows for achieving significant clinical benefits, with minimized risk of disease progression or severe adverse reactions. In the era of the COVID-19 pandemic, metronomic chemotherapy, with its efficacy and excellent safety profile, represents an extremely convenient and safe treatment option [7, 13].

Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Bisphosphonate treatment as a safe choice for treating lung metastases of recurrent giant cell tumor of bone

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ABSTRACT

Giant cell tumor (GCT) accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors. This case report presents the case of a 17-year-old female with a recurrent giant cell tumor and lung metastases. The patient received bisphosphonate therapy instead of surgery. The use of zoledronic acid for lung metastases from GCT may have conservatively improved clinical symptoms and radiological assessments can be achieved.

Key words: bisphosphonate, giant cell tumor, recurrence

Oncol Clin Pract 2023; 18, 3: 178–183

Introduction

Giant cell tumor (GCT) accounts for 5% of all primary bone tumors and 20% of benign skeletal tumors. It is common in young adults aged between 20 and 40 years, with a slightly higher incidence in females. GCT metastases to the lung, lymph nodes, liver, soft tissues, brain, mediastinum, scalp, or kidney are fairly rare. The recurrence rate is only about 3%. Inappropriate surgical treatment may lead to increased osteolysis and destruction of the joints adjacent to the primary site. The currently available treatment options for these metastases are metastasectomy, chemotherapy, denosumab, interferon, or bisphosphonates [1, 2]

In this case report, we aimed to evaluate outcomes for a GCT patient with metastases to the lung, who received long-term oral bisphosphonate. The purpose of this study is to show that bisphosphonate is a safe and viable option to achieve good outcomes.

Case presentation

A 17-year-old female presented to the Orthopaedic Clinic of Sanglah General Hospital Denpasar Bali. The patient reported a painful lump on her ankle that she had first noticed 8 months earlier. This issue started with a small lump on the left ankle which gradually grew. At the same time, the pain gradually worsened especially in the preceding 5 months (Fig. 1). At the same time, she suffered from weight loss. She presented with swelling, local tenderness, and a 6 x 6 cm mass with an irregular margin at her distal left tibia. Radiological investigation using plain X-ray and magnetic resonance imagining (MRI) of the ankle was then performed, revealing lytic lesion and cortical destruction on the epi metaphysis of the distal tibia (Fig. 1, 2) without any metastases to the lung (Fig. 3) — suggesting Enneking stage 3 or Campanacci grade III giant cell tumor of the distal tibia.

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Figure 1. Clinical picture and radiography examination of the left ankle

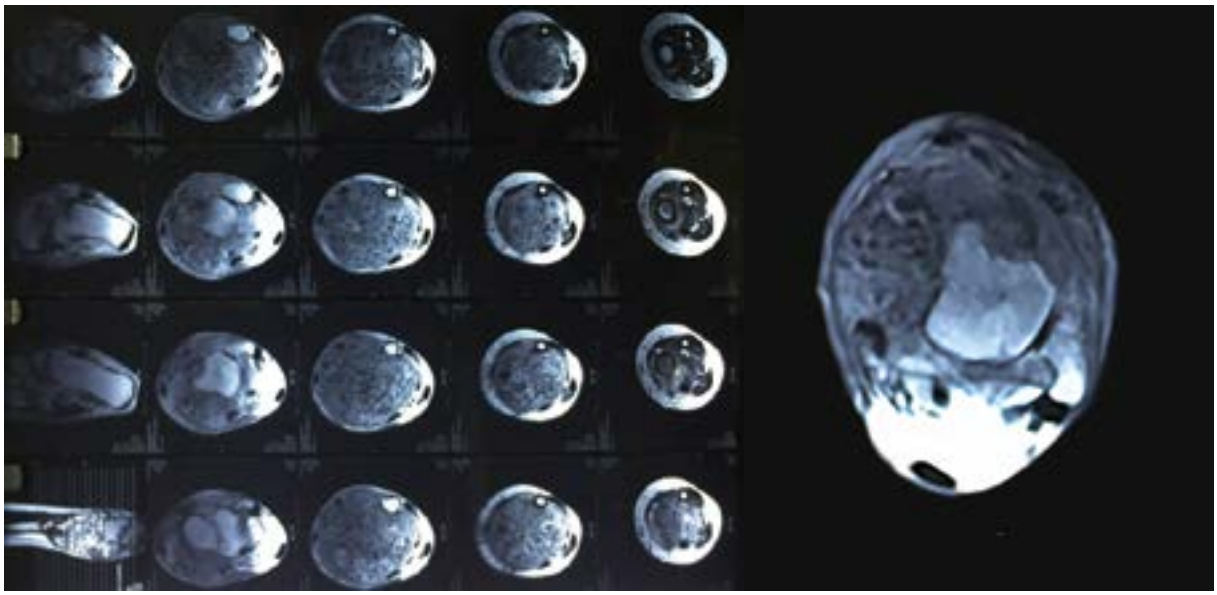

Figure 2. Magnetic resonance imaging of the ankle showed cortical destruction of the distal left tibia with minimum soft tissue involvement

The patient was then admitted for inpatient care and first underwent an open biopsy and frozen section. The histopathology analysis found dense proliferation of spindle mononuclear cells, which confirmed the suspicion of GCT. After this diagnosis, we performed extensive resection followed by fibula and ankle arthrodesis tibial reading as a curative treatment for the lesion (Fig. 4). The post-operative X-ray is shown in Figure 5. The patient also underwent bisphosphonate treatment for 18 months after the resection procedure to prevent any local recurrence and metastases.

Two years after the surgery, the patient returned to the hospital with a new complaint of shortness of breath aggravated by activity and slightly reduced after rest. A chest X-ray and computed tomography (CT) scan were performed to assess whether any lung metastases had occurred. The chest X-ray showed coin lesions with suspected embolism or metastasis while the CT-scan of the chest revealed multiple enhanced solid nodules in the perihilar segment of the lung. An X-ray of the left ankle also showed lytic lesions at the distal region indicating recurrence (Fig. 6). Cardiothoracic surgeons were consulted for any possible metastasectomy procedure, but there was a considerable risk. Therefore, the patient opted for conservative treatment for the lung metastases, with further 5 months of bisphosphonate

therapy. For the primary tumor, the patient underwent a curettage procedure with highspeed burr and phenol followed by bone cement filling to repair the defect (Fig. 6, 7). She then received 4 mg of zoledronic acid in 6 cycles and was able to walk pain-free with no crutches after 6 months.

The patient underwent bisphosphonate therapy that consisted of a monthly dose of 4 mg zoledronic acid for 6 consecutive months following the metastasis discovery.

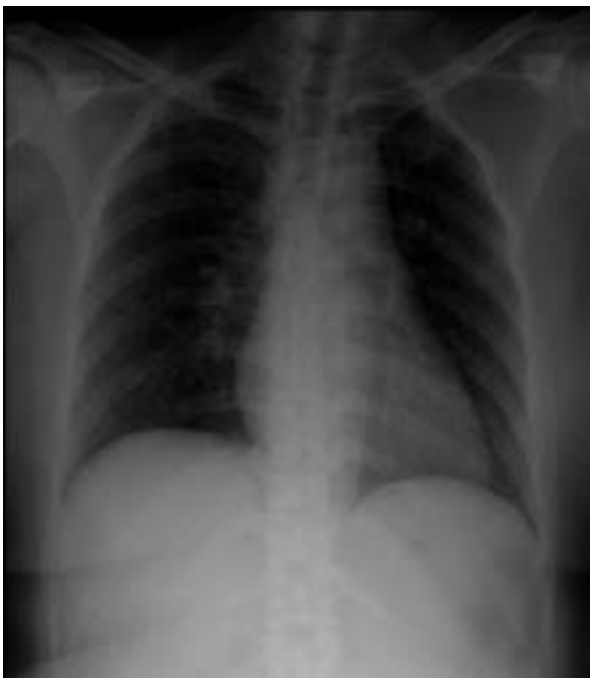

Figure 3. Chest X-ray

Five months follow-up after initiation of bisphosphonate therapy showed a favorable outcome based on clinical and radiological evaluations. The patient had no complaints about shortness of breath and has been able to do daily activities without any difficulty. A chest X-ray and CT scan showed significant differences after zoledronic acid therapy (Fig. 8, 9).

Discussion

Local recurrence of GCT is rather common, ranging from 10 to 26.9%, with extra-compartmental (soft tissue) extension and tumor grade considered the most significant risk factors [3]. With regards to metastases, the lungs are the m ost common site where GCT metastases frequently occur. Its incidence is estimated to be as much as 5% of bone GCT, especially in younger patients with grade 3 Enneking disease [4–6].

In this case, a CT scan identified pulmonary emboli which were visible as multiple enhanced solid nodules in almost all segments of the lung. This patient was placed under the joint care of thoracic and vascular surgeons. Following discussions with the patient, we decided to treat the metastases with conservative treatment instead of a surgical procedure. Follow-up conducted 5 months after the initiation of conservative bisphosphonate zoledronic acid therapy found significant improvement of the lung lesions. This is in line with previous findings by Zekri et al. [7], which showed that zoledronic acid's antitumor effect is mediated through inhibition of tumor cells proliferation, induction of apoptosis, synergistic/additive to the inhibitory effect of cytotoxic agents,

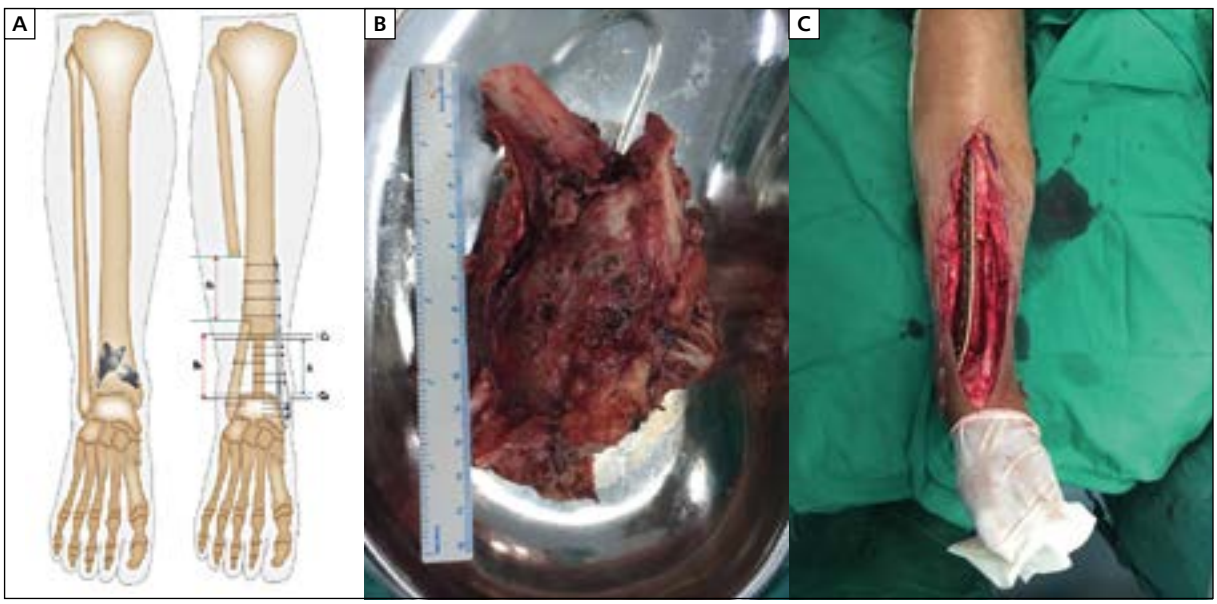

Figure 4. Clinical picture of the surgery showing; **A.** Pre-operative planning; **B.** The resected tumor with a 2 cm margin of healthy soft tissue; **C.** Clinical condition after fixation with autologous strut graft from the fibula

inhibition of angiogenesis, decrease of tumor cells adhesion to the bone, decrease of tumor cells invasion and migration, disorganization of cell cytoskeleton and activation of a specific cellular antitumor immune response.

Bisphosphonates are stable analogs of inorganic pyrophosphate in which the oxygen atom of the P-O-P bond is replaced with a non-hydrolyzable P-C-P bond. Bisphosphonates inhibit osteoclast activity by several mechanisms which depend largely on their chemical structure. Bisphosphonates have been shown to induce apoptosis of tumor cells and inhibit tumor cell growth of a variety of tumor cell types [8].

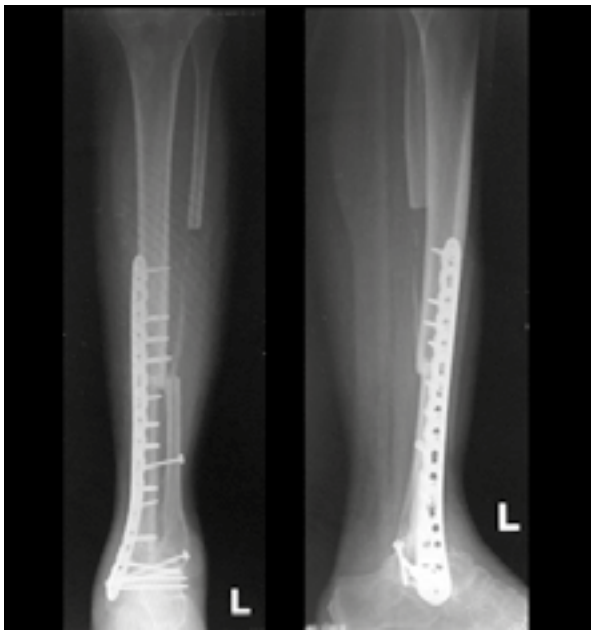

Figure 5. Post-operative X-ray

Zoledronic acid has a high affinity for mineralized bone accumulating rapidly after intravenous administration and localizing preferentially at sites of high bone turnover. It is thought to be internalized during bone resorption via the endocytic activity of osteoclasts and inhibits bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) and preventing protein prenylation. The binding affinity of zoledronic acid for hydroxyapatite was higher than that of other bisphosphonates (binding affinity constants of $3.47\ 9\ 10^{-6}$ mol/L *vs.* 2.94, 2.36, 2.19, 1.19 and $0.72\ 9\ 10^{-6}$ mol/L for alendronic acid, ibandronic acid, risedronic acid, etidronic acid, and clodronic acid, respectively) [9]. Zoledronic acid has also been considered a reasonable, effective treatment for unresectable lesions [7, 10].

Unlike bisphosphonate, the optimal duration, long-term safety, maintenance dose, and optimum indications of denosumab in GCT treatment remain to be elucidated. A recent in-depth review by Li et al. [11] warns that denosumab therapy of GCT of the bone (GCTB) should be applied with caution. Furthermore, denosumab is also still associated with a probable increase of local recurrence in patients treated with curettage [11].

In this study, we conducted bisphosphonate therapy using zoledronic acid in a patient who had lung emboli due to metastases of GCT. Bisphosphonate has shown a promising result in treating metastases of GCT. The anti-osteoclast effect of bisphosphonates and their ability to prevent bone resorption make bisphosphonates a potential treatment for GCT, and several studies have confirmed its efficacy [10]. However, in this study the patient had a recurring case of GCT in the left ankle based on clinical symptoms and radiographic examination. The study conducted by Xu et al. [12] showed that the recurrence rate of GCT was 2.1%, and the mean interval time was 11.3 ± 4.1 months with a range from 5–17 months.

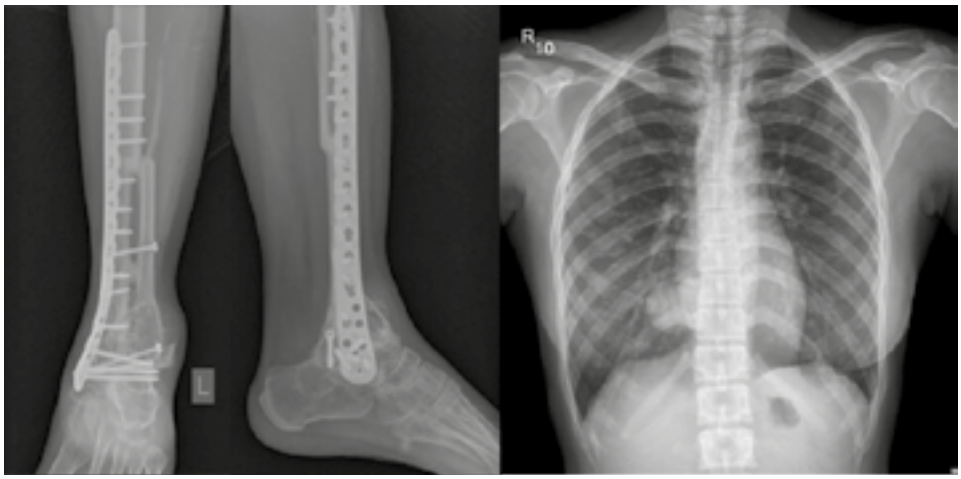

Figure 6. Chest and ankle X-rays taken 2 years after the first surgery, showing recurrence at the initial primary site with metastases to the lung despite receiving 6 months of bisphosphonate treatment

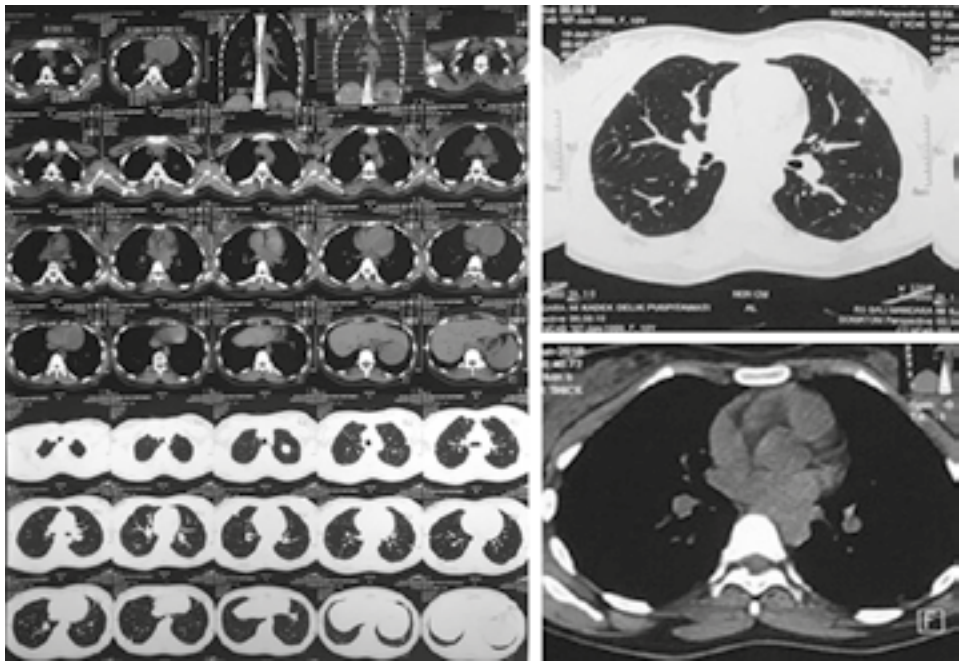

Figure 7. Chest computed tomography scan after 2 years after surgery, showing metastatic nodules at almost all lobes of the lung

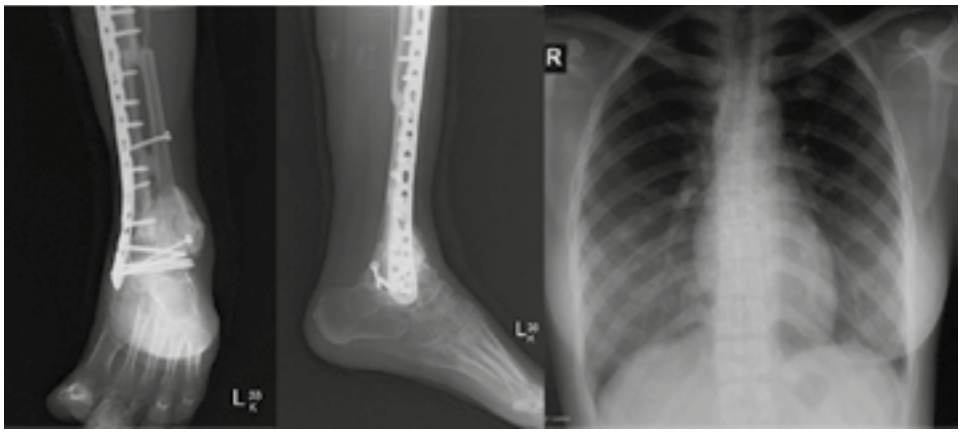

Figure 8. Chest and ankle X-Ray post-surgical bone graft and bisphosphonate therapy

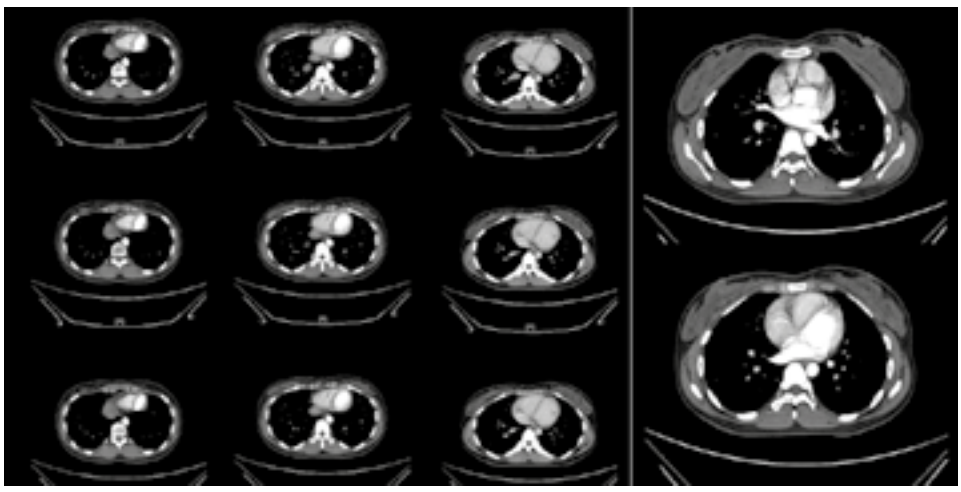

Figure 9. Chest CT scan after bisphosphonate therapy

In a previous study reported by Balke et al. [13], the authors examined clinical and radiological outcomes of bisphosphonate treatment in 25 cases of aggressive primary, recurrent, and metastatic giant cell tumors from 4 European centers. They reported no signs of progression or increase in the size or number of lung metastases in GCT patients who were treated with bisphosphonates. The use of bisphosphonate to treat pulmonary metastases in GCT has also been reported by Dubey et al. in 2019 [14]. They reported that the usage of bisphosphonates successfully reduced chest pain and controlled tumor growth, as soon as 3 months after therapy.

In our case, bisphosphonate therapy has been successful in controlling the lung metastases of the GCT. Even though this finding is based only on observation, we argue that it is still a viable safe first-line method of managing patients with lung metastases from GCBT [14, 15], We propose that surgical metastasectomy could be delayed for such metastases and reserved for cases that are resistant to bisphosphonate therapy.

Conclusion

Improvement in clinical symptoms and control of tumoral growth in the case of lung metastases of GCT could be achieved conservatively by using zoledronic acid.

Consent

Written informed consent was obtained from the patient for being included in the study and its publication.

Ethics statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Author contributions

N.H.K.: study concept and design, performed surgery, final editing and publication; K.P.B.S.: data collection and drafting; W.I.G.E.: performed surgery.

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Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Leptomeningeal metastasis in primary uterine cervical cancer: a rare case and review of the literature

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ABSTRACT

Objectives. Leptomeningeal metastasis (LM) of primary uterine cervical cancer is rare and treatment options are limited. In this case report and literature review, we aimed to present a patient with cervical cancer with LM and discuss previously reported cases in the literature.

Case presentation. Our case was a 58-year-old patient who was initially diagnosed with metastatic primary uterine cervical cancer and treated with chemotherapy and chemoradiotherapy. During follow-up, she developed neurological symptoms, and LM was detected in the craniospinal regions. Cerebrospinal fluid cytology examination has confirmed metastatic disease. The patient was treated with concurrent intrathecal methotrexate and whole-brain radiotherapy (WBRT). A good clinical and cytological response was obtained. However, while intrathecal methotrexate was being continued after WBRT, she succumbed to hematological toxicity before the radiological response could be evaluated.

Conclusions. LM is an extremely rare and catastrophic distant spread pattern in patients with cervical cancer. In the literature, a total of 26 patients were reported up to date. Median survival after detection of LM was nine weeks, including our case. Multimodal treatment combinations such as systemic and intrathecal chemotherapy and radiotherapy (RT) were used. However, most of these reports did not have detailed information about toxicity. Despite the combined use of aggressive treatment modalities, patients have limited survival and very high risks of hematologic toxicity. Concurrent use of intrathecal chemotherapy and radiotherapy should be avoided due to increased risk of morbidity.

Key words: cervical cancer, leptomeningeal metastasis, radiotherapy

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Introduction

Cervical cancer is the most common gynecological cancer worldwide and a significant health problem, particularly in underdeveloped countries [1]. At the time of diagnosis, approximately 44% of patients have localized disease, 36% have a regional disease, and 16% have distant metastasis (DM) [2]. In metastatic disease, systemic chemotherapy and palliative radiotherapy (RT) may be beneficial.

Uterine cervical cancer most commonly metastasizes to the lungs [3]. Leptomeningeal metastasis (LM) is an extremely rare site of DM in patients with uterine cervical cancer but is more common in lung cancer, breast cancer, and melanoma [4]. Leptomeningeal metastasis often causes neurological symptoms and is

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usually observed on magnetic resonance imaging (MRI). Cytological examination of the cerebrospinal fluid (CSF) sample taken by lumbar puncture is required for accurate diagnosis unless there is a contraindication. Aggressive treatment modalities, such as a combination of intrathecal chemotherapy (ITC) and RT, are often used for treatment [5]. However, the data on the management of LM in patients with uterine cervical cancer in the literature is scarce.

In this case report, we present a case of a patient with primary uterine cervical cancer who developed LM. The primary aim of this case report and literature review is to share the treatment details for this patient and discuss and compare them with previous reports.

Case presentation

A 58-year-old female was admitted in March 2020 to the Department of Pulmonology with shortness of breath and weight loss lasting two months. Her medical, family, and psycho-social history was unremarkable. The patient underwent computed tomography (CT) of the thorax and abdomen which revealed multiple mediastinal lymph nodes (LN), uterine cervical mass, bilateral parailiac LNs, and suspicious hepatic lesions. The patient was then directed to the Gynecologic Oncology Department. In the gynecological examination under general anesthesia, a necrotic and bleeding tumoral mass of 3 cm was detected in the uterine cervix, and the right parametrium was infiltrated. A pathology study of the cervical biopsy revealed a squamous cell carcinoma (SCC) of the uterine cervix. A positron emission tomography (PET)/CT was performed for staging purposes, and extensive bone and multiple liver metastases were detected in addition to the primary mass (38 × 51 mm) in the uterine cervix and left common iliac, right internal iliac, and left external iliac LNs.

The patient was then evaluated by the Gynecologic Oncology tumor board, and a decision was made to administer systemic therapy with cisplatin (50 mg/m^2, total dose: 80 mg every three weeks), paclitaxel (180 mg/m^2, total dose: 288 mg), and bevacizumab (15 mg/kg, total dose: 870 mg). Following 6 cycles, a very good metabolic response, both in the primary and metastatic sites, was observed on the PET/CT, and definitive chemoradiotherapy was planned for the primary site and regional lymphatics after reassessment by the tumor board. A 50.4 Gy volumetric-modulated arc therapy to the uterus, cervix, proximal 1/3 of the vagina, parametrial and paravaginal sites, and bilateral common, internal and external iliac, obturator and presacral lymphatics in a 1.8-Gy fraction dose with concurrent cisplatin of 40 mg/m^2/week (total dose: 60 mg) was planned and started in August 2020. However, on the MRI for brachytherapy preparation during external beam radiotherapy (EBRT), the liver metastases progressed even though the primary cervical mass and the LNs regressed, and the EBRT was stopped at 45 Gy after consideration by the tumor board. The board decided to use additional chemotherapy after completion of intracavitary brachytherapy. A total dose of 28 Gy brachytherapy was administered in 4 fractions. Following this, the patient started to receive the same chemotherapy regimen again in September 2020.

After the third cycle, the PET/CT in December 2020 revealed a complete metabolical response. Chemotherapy was stopped but bevacizumab was continued at the same dose. However, 3 months after the chemotherapy was stopped in March 2021, liver metastases progressed on the abdominal CT and weekly carboplatin (180 mg) and paclitaxel (125 mg) was initiated while bevacizumab was stopped. Following the 10th week of this regimen, the CT revealed a partial regression in the liver metastases. Two weeks after the last chemotherapy in July 2021, the patient reported pain in the right femur, and an X-ray revealed a sclerotic lesion in the distal femur. Because of the risk of pathological fracture, the patient underwent a bone curettage, cementation, and prophylactic fixation with a plaque, and a pathology examination revealed an atypical chondroid tumor of the bone. During the perioperative period, the patient could not receive any systemic therapy.

Approximately 1 month after the operation in August 2021, the patient started to report a diffuse headache and motor weakness in bilateral legs. The craniospinal MRI revealed a total of 5 cortical-meningeal metastases in the supra and infratentorial regions and extensive spinal LM, most prominent in the conus medullaris with diffuse thickening and nodular contrast enhancement in the cauda equine fibers (Fig. 1). Malignant epithelial cells were also detected in CSF cytology. which were reported as SCC metastasis of the uterine cervix. As an initial intervention, high-dose dexamethasone was administered. At this point, 2 different treatment approaches were considered by the radiation oncologists and medical oncologists; either a craniospinal irradiation (CSI) or cranial RT with intrathecal chemotherapy. Considering the possible severe toxicity of CSI, we decided to administer intrathecal methotrexate and cranial RT. Thereupon, 3 cycles of 15 mg intrathecal methotrexate were administered twice a week. Then, 30 Gy whole brain radiotherapy (WBRT) was applied in 10 fractions with concurrent 2 cycles of 15 mg of intrathecal methotrexate once a week between September 16 and 30, 2021.

Whole brain radiotherapy was well tolerated without any severe acute toxicity. A good clinical response was obtained afterward. The patient's headache completely disappeared, and her motor weakness decreased considerably. Intrathecal methotrexate was continued

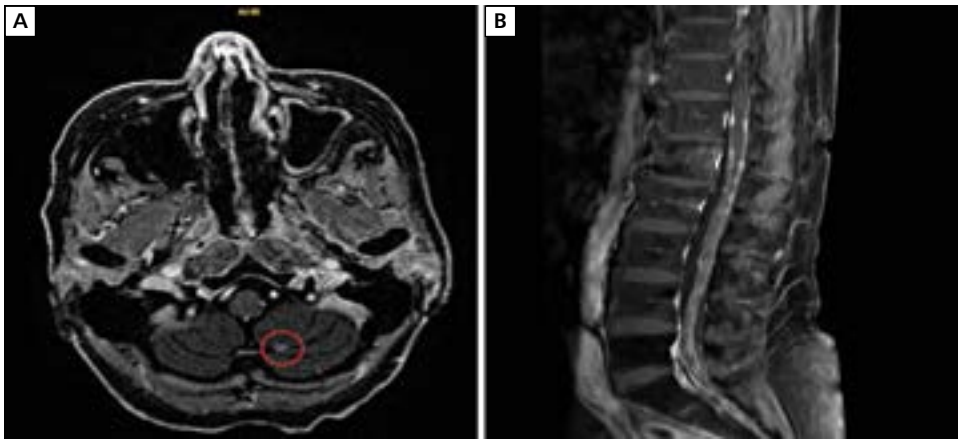

Figure 1. Cranial (**A**) and spinal (**B**) leptomeningeal metastases on magnetic resonance imaging; **A.** Cortical-meningeal metastasis in the left cerebellar region (red circle); **B.** Extensive spinal leptomeningeal metastasis in the lumbar and sacral regions

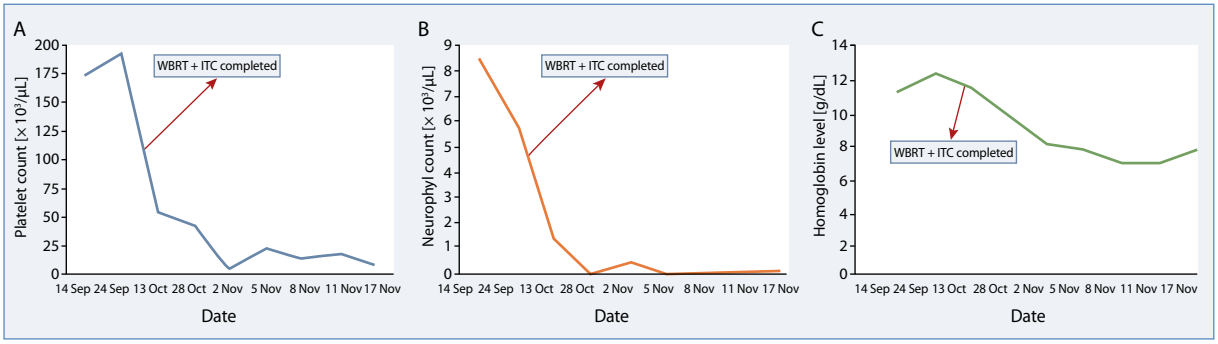

Figure 2. Hematologic parameters of the patient during treatment for leptomeningeal metastases; **A.** Platelet count/μL; **B.** Neutrophil count/μL; C. Hemoglobin levels; WBRT — whole brain radiotherapy; ITC — intrathecal chemotherapy

after WBRT for 6 weeks twice a week until CSF cytology was negative on October 28, 2021. No severe neurological toxicity was observed in the remaining life period of the patient. However, the patient developed severe thrombocytopenia and neutropenia during ITC and had to be supported by platelet suspensions and granulocyte-macrophage colony-stimulating factor. The data on the number of thrombocytes and neutrophils and the level of hemoglobin are shown in Figure 2. At the end of the third month, the patient succumbed to pancytopenia, febrile neutropenia, and septic shock due to bacterial and fungal pneumonia on November 17, 2021 before the radiological response could be evaluated.

Discussion

In patients with primary uterine cervical cancer, the incidence of DM at the time of diagnosis is approximately 16%, and the most common site is the lungs [2, 3]. Metastasis to the central nervous system is unusual. The rate of parenchymal brain metastasis of uterine cervical cancer was reported as 0.4–2.3% in the literature [6]. Leptomeningeal metastasis is even rarer, and the incidence was reported as 0.03% [7].

To the best of our knowledge, 26 cases have been reported in the literature so far, and we report the 27th patient in this case study [7–27]. We included our patient together with these 26 patients and recalculated the characteristics. Table 1 summarizes the characteristics of these 27 patients. Their median age was 47 years (range: 30–64 years), and 22% of these patients had DM at the time of diagnosis. The most common histological subtype was SCC. The latest diagnosis of LM was reported 17 years after the initial diagnosis; however, in general, LM developed within the first one to five years after initial treatment. Our patient developed LM 17 months following the initial diagnosis while under chemotherapy due to extensive metastatic disease.

Leptomeningeal metastasis of solid tumors often presents with neurologic symptoms and is usually detected by MRI. Most of the aforementioned 27 patients had neurologic symptoms consistent with lesion localization, the most common being a headache. Although

Table 1. Patient, tumor and treatment characteristics of cervical cancer patients with leptomeningeal metastasis (LM)

Patient no.	Histology	Initial Stage	Primary treatment	Other metastasis	Time to LM diagnosis	Treatment for LM	RT field	C regimen	Survival after LM	Toxicity
#1 (7)	SCC	Localized	N/A	LNs (cervical, pelvic)	25 weeks	N/A	N/A	N/A	17 weeks	N/A
#2 (7)	SCC	Localized	N/A	Brain, buttock	190 weeks	N/A	N/A	N/A	9 weeks	N/A
#3 (7)	ASC	Localized	N/A	Lung, brain	228 weeks	N/A	N/A	N/A	46 weeks	N/A
#4 (7)	AC	Localized	N/A	Cervix, endometrium	9 weeks	N/A	N/A	N/A	14 weeks	N/A
#5 (8)	NEC	Localized	Surgery SC	Breast, lung, LNs (mediastinum, abdominal)	19 months	RT	Cranial	None	2 weeks	None
#6 (9)	SCC	Localized	Surgery RT	LNs (pelvic), Bone	836 weeks	RT	N/A	None	12 weeks	N/A
#7 (10)	SCC	Localized	RT	LNs (pelvic, PA)	39 months	SC ITC	Craniospinal	IT-MTX, S-MeCCNU	2 weeks	Facial paralysis, stomatitis, pancytopenia
#8 (11)	SCC	Metastatic	SC RT	Lung	6 weeks	Supportive care (analgesics)	None	None	2 weeks	None
#9 (12)	SCC	Localized	Surgery SC	N/A	56 weeks	RT	Cranial	None	4 weeks	N/A
#10 (13)	AC	Localized	RT	LNs (PA, SCF)	2 years	ITC RT	Cranial	IT-MTX	1 week	N/A
#11 (14)	ASC	Localized	RT	Bone	52 weeks	RT SC	Cranial	S-Cisplatin + Topotecan	8 weeks	Septic shock, DIC
#12 (15)	SCC	Localized	CRT	LNs (SCF)	2 years	ITC	None	IT-MTX	13 weeks	None
#13 (16)	ASC	Metastatic	SC	None	At diagnosis	ITC RT SC	Cranial	IT-MTX, S-carboplatin	35 weeks	N/A
#14 (17)	SCC	Localized	Surgery CRT	Brain, lung, LNs, vagina	58 weeks	RT	Cranial	None	3 weeks	N/A
#15 (18)	ASC	Localized	CRT	Liver	31 months	RT	Craniospinal	None	8 weeks	N/A
#16 (18)	NEC	Localized	CRT	Brain, bone, liver, mediastinum	19 months	RT SC	Cranial & Focal Spinal	S-Cisplatin + Etoposide	28 weeks	Infectious toxicity
#17 (19)	SCC	Metastatic	N/A	None	At diagnosis	N/A	N/A	N/A	N/A	N/A
#18 (20)	SCC	Localized	CRT	Bone, sciatic nerve	10 months	N/A	N/A	N/A	N/A	N/A
#19 (21)	SCC	Localized	CRT	LNs (PA, SCF)	34 months	ITC RT	Cranial	IT-MTX IT-Thiotepa	26 weeks	Cognitive deterioration
#20 (22)	SCC	Localized	CRT	Lung, liver, peritoneum, skin	35 weeks	RT	Cranial & Focal Spinal	None	N/A	N/A
#21 (23)	NEC	N/A	N/A	None	At diagnosis	N/A	N/A	N/A	N/A	N/A
#22 (24)	SCC	Localized	Surgery	LNs (PA, pelvic)	13 years	RT ITC	Cranial	IT-Thiotepa	9 weeks	None
#23 (25)	NEC	Metastatic	SC	Bone, LNs (pelvic, PA)	2 weeks	None	None	None	2 weeks	None
#24 (26)	AC	Localized	CRT SC	LNs (PA, pelvic)	10 months	Palliative therapy	None	None	7 weeks	None
#25 (27)	SCC	Metastatic	SC	LNs (pelvic, PA)	At diagnosis	RT SC	Cranial	S-Paclitaxel + Carboplatin	20 weeks	None
#26 (27)	SCC	Localized	Surgery RT	Lung, LNs (neck, mediastinum, axilla)	240 weeks	RT	Cranial	None	3 weeks	None
#27 (our case)	SCC	Metastatic	SC CRT	Bone, liver, LNs (pelvic, PA)	68 weeks	ITC RT	Cranial	IT-MTX	12 weeks	Pancytopenia

AC — adenocarcinoma; ASC — adenosquamous carcinoma; C — chemotherapy; CRT — chemoradiotherapy; DIC — disseminated intravascular coagulation; IT — intrathecal; ITC — intrathecal chemotherapy; LN — lymph node; MeCCNU — semustin; MTX — methotrexate; N/A — not available; NEC — neuroendocrine carcinoma; PA — paraaortic; RT — radiotherapy; SC — systemic chemotherapy; SCC — squamous cell carcinoma; SCF — supraclavicular fossa

MRI is very valuable in detecting seeding metastases, the gold standard is the cytological examination of CSF via lumbar puncture unless there is a contraindication, such as a skin infection in the puncture site, bleeding diathesis, cardio-respiratory instability, or increased intracranial pressure.

There is no effective or successful standardized treatment in patients with LM that has a poor prognosis. Intrathecal and systemic chemotherapy with various agents and WBRT with or without spinal RT were used in the cases reported so far. In general, the role of WBRT in the treatment of LM is to provide symptom palliation due to cranial involvement and improve neurological functions. Focal spinal RT may also be considered for symptom palliation in cauda equina syndrome or symptomatic gross-nodular spinal LM. Craniospinal irradiation is mostly used in the central nervous system involvement of various hematological malignancies [28]. CSI is typically not appropriate for LM of solid tumors, particularly concurrent with ITC, due to the high risk of toxicity, short life expectancy, and low likelihood of a significant benefit. On the other hand, CSI can also be applied in LM of solid tumors with acceptable toxicity rates [29]. Chemical meningitis and leukoencephalopathy are potentially serious complications of ITC administration. Concurrent use of ITC and RT raises even higher concerns because of the risk of toxicity. In a prospective study involving 59 patients with various cancers, grade 3–5 toxicity was reported in 20% of patients who received concurrent intrathecal methotrexate and RT for LM [30]. Although severe neurological toxicity has not been reported most probably due to low survival rates in patients with cervical cancer and LM, the possibility of severe toxicity due to concurrent treatment should not be underestimated.

Unlike systemic chemotherapy, the hematological toxicity of ITC is not overemphasized. However, intrathecally administered methotrexate can enter the systemic circulation via the choroid plexus and cause systemic effects such as bone marrow suppression [31]. Kose et al. [32] reported that severe hematologic toxicity may develop after intrathecal methotrexate. The majority of case reports on cervical cancer patients with LM did not mention treatment-related toxicity or the reason for death in these patients. In Weed et al. [10] study, pancytopenia was reported in a patient during intrathecal administration of methotrexate. However, the details of this toxicity were not given. In two other studies, an infectious complication was mentioned as septic shock and pneumonia, similarly without any details [14, 18]. We think that this infectious toxicity could have been related to neutropenia. Although no radiologic response could be evaluated, our patient had improved neurologic symptoms but succumbed to treatment toxicity. We believe that in other case reports without toxicity details, at least several patients could have developed severe hematologic toxicity and even succumbed to this toxicity.

Despite these aggressive treatment combinations, median survival after detection of LM was nine weeks (range: 1–46 weeks) in the 27 patients in the literature. Since patients with LM already have a limited life expectancy, every effort has to be taken in order not to impair their quality of life and cause more neurological toxicity while trying to regress the present neurologic symptoms. Although there are no high-quality data available to allow us to say that concurrent ITC and RT are safe, intrathecal methotrexate and WBRT were concurrently administered in our patient without severe neurological toxicity. It should be kept in mind that the time required for delayed neurological toxicities to occur may not have been reached due to the limited survival rate of the patient. In addition, the patient succumbed to pancytopenia and related sepsis less than 3 months after treatment. Although it is not clear whether the factor causing hematological toxicity was the combination of ITC and RT in our case, it seems highly possible.

Conclusion

There is insufficient high-quality evidence to guide the treatment of LM in patients with uterine cervical cancer. Despite the combined use of aggressive treatment modalities such as RT and ITC, the prognosis is quite poor. Improving the quality of life in this patient group with very low survival rates should be one of the most important goals, and the outcomes of treatment and toxicity should be well-balanced. In order not to cause severe hematologic toxicity, ITC with concurrent RT, even a focal WBRT should be avoided. Furthermore, de-intensifying the number of ITC to weekly doses can minimize hematologic toxicity.

Ethics statement

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patients relative for publication of the details of their medical case and any accompanying images.

Author contributions

All of the authors made significant contributions to this paper regarding the design of the manuscript, writing, and critical review in such a way that they participated sufficiently in the work to assume responsibility for the content.

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Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Replacement of ALK inhibitors as an effective strategy for reducing drug toxicity in non-small cell lung cancer patients with *ALK* gene rearrangement

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ABSTRACT

This case report examines the effects of replacement of anaplastic lymphoma kinase inhibitor (ALKi) as a strategy to reduce drug toxicity in patients with non-small cell lung cancer (NSCLC) with *ALK* gene rearrangements. A 61-year-old female patient with lung adenocarcinoma encountered difficulties in ALK abnormalities diagnosis: the expression of abnormal ALK protein was not detected by the immunohistochemistry (IHC) assay, but *ALK* gene rearrangement was present in next generation sequencing (NGS) and fluorescence *in situ* hybridization (FISH) assays. The patient was initially treated with second-generation ALKi (alectinib). However, the patient experienced severe hepatotoxicity. She was successfully switched to brigatinib (another second-generation ALK inhibitor). During brigatinib therapy, a transient increase in creatinine kinase concentration was observed, which required brigatinib dose reduction. Effectiveness of both anti-ALK agents was observed (partial response to treatment, followed by disease stabilization). This case report illustrates the difficulties in diagnosing *ALK* gene rearrangements and the possibility of replacing ALK inhibitors without compromising treatment efficacy.

Key words: *ALK* rearrangement, alectinib, brigatinib, hepatotoxicity, lung adenocarcinoma

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Introduction

The *anaplastic lymphoma kinase* (*ALK*) gene rearrangement occurs in approximately 4.5% of non-small-cell lung cancer (NSCLC) patients. It is found mainly in young and non-smoking patients with adenocarcinoma. It is the third most common driver alteration in lung adenocarcinoma after mutations in the *kirsten rat sarcoma virus* (*KRAS*) *and epidermal growth factor receptor* (*EGFR*) genes. There are different fusion partners for the *ALK* gene, and some variants are very rare. The most common is the fusion of exon 13 of the *echinoderm microtubule-associated protein-like 4* (*EML4*) gene and exon 20 of the *ALK* gene (variant 1). Slightly more seldom, exon 20 of the *EML4* gene is fused with exon 20 of the *ALK* gene (variant 2) or exon 6 of the *EML4* gene with exon 20 of the *ALK* gene (variant 3a or 3b). The genetic fusion partner for the *ALK* gene and the fusion variant may determine the usefulness of different methods of *ALK* gene diagnosis and the effectiveness of treatment with ALK inhibitors (ALKi) [1].

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Three generations of ALKi are available for locally advanced or advanced NSCLC patients with *ALK* gene rearrangement. The first-generation crizotinib, which is characterized by relatively low efficacy and poor penetration to the central nervous system (CNS) is rarely used. Alectinib, brigatinib, ceritinib, and ensartinib belong to the second generation of ALKi. These drugs are more effective than crizotinib, especially in the treatment of CNS metastases, and can be used both in the first line of treatment and after crizotinib treatment failure. The third generation of ALKi is lorlatinib — it has the highest CNS penetration and high intracranial and extracranial efficacy. Lorlatinib can be used in the first-line treatment and patients with failure of first- and second-generation ALKi therapy. All these drugs differ in their toxicity profile [2].

The patient presented in this report experienced ALKi treatment toxicity, which was managed by switching the inhibitor. The patient also had difficulties in the diagnosis of *ALK* gene rearrangement probably due to the presence of a rare EML4-ALK fusion variant. The patient gave her written consent to participate in research following approval of the local bioethics committee at the Medical University of Lublin (No. KE-0254/160/2021)

Case report

A 61-year-old female patient, a former cigarette smoker, was unsuccessfully treated in July 2021 for bronchitis with a persistent dry cough. Comorbidities included multinodular thyroid goiter, hypertension, anemia, neutropenia, and type 2 diabetes. The patient had a good performance status. A chest X-ray revealed the presence of pleural effusion on the left side. The presence of pleural effusion was confirmed on computed tomography (CT) imaging, and a tumor in the left hilum, the prevertebral soft-tissue lesion measuring 34 × 26 mm at the carina level and fluid in the pericardium were revealed. In August 2021, a left-sided diagnostic thoracotomy was performed with partial resection of rib VI and decortication of the left lung. In the material from the pleura, infiltration of lung adenocarcinoma with the expression of cytokeratin 7 and 19 (CK7 and CK19) and epithelial membrane antigen (EMA) was found. This material did not show mutations in *EGFR* gene which was examined by real-time PCR method with Entrogen reagent kit and COBAS Z480 real-time equipment. ALK abnormal protein expression was not detected by immunohistochemistry (IHC) method using the Ventana D5F3 antibody clone and BenchMark GX autostainer, *ROS1* gene rearrangement was excluded by fluorescent in situ hybridization (FISH) method using ZytoVision ROS1 Dual Color Break Apart Probe. Programmed death ligand 1 (PD-L1) expression was visualised on < 1% tumor cells and was examined by IHC method using Ventana SP263 antibody clone and BenchMark GX autostainer.

A decision about performing in-depth diagnostics was made. In September 2021, a positron emission tomography–computed tomography (PET-CT) examination was performed. Pleural effusion accumulated FDG [^{18}F-FDG, (^{18}F) 2-fluoro-2deoxy-D-glucose] in the left costophrenic angle, where maximum standardized uptake value (SUV_{max}) was 3.3. Numerous, metabolically active nodules were present in the left pleura. The primary lesion measuring 65 × 45 mm was present at the level of the lower part of the left hilum (SUV_{max} = 15.7 with a central cold area, indicating tumor disintegration). A prevertebral soft-tissue lesion modulating the lumen of the esophagus shown on CT did not accumulate FDG, suggesting a reservoir of encapsulated, thick fluid. A 13 × 10 mm nodule was present at the proximal part of the descending aorta (SUV_{max} = 13.0). Numerous enlarged and metabolically active lymph nodes were visualized in the lower part of the left lung hilum (22 × 13 mm, SUV_{max} = 15.1), aortopulmonary window (17 × 12 mm, SUV_{max} = 13.5), pulmonary trunk (15 × 13 mm, SUV_{max} = 9.0), at the apex of the heart (20 × 12 mm, SUV_{max} = 12.6), supraphrenic and paraspinal on the left side (20 × 14 mm, SUV_{max} = 10.7). Increased FDG uptake was also observed postoperatively in the stump of rib VI (SUV_{max} = 5.8). On this basis, stage IVA of lung adenocarcinoma (pT4N2M1A according to the 8th Edition of TNM in Lung Cancer) was diagnosed (Fig. 1A–C).

In addition, RNA-based next-generation sequencing (NGS) was performed on the material obtained during thoracotomy to qualify the patient for a clinical trial. The assay used RNA isolated from the formalin-fixed paraffin-embedded (FFPE) material. The first fusion variant of the *EML4-ALK* gene was detected (fusion of exons 13 and 20). The FISH method (using Vysis ALK Break Apart FISH Probe Kit) was performed due to discrepancies between the IHC and NGS results in the assessment of the presence of *ALK* gene rearrangements. Single red signals were found in 20% of tumor cell nuclei, which allowed for recognition of *ALK* gene rearrangement.

In November 2021, alectinib therapy at the standard dose of 600 mg twice a day was started. During the first month, the treatment was interrupted for a week due to the onset of herpes zoster, which required acyclovir therapy. However, on the first follow-up CT scan, partial remission was observed. The primary tumor was reduced to 25 mm in the longest diameter (baseline — 65 mm). Pleural effusion was encapsulated. Mediastinum and subaortic lymph nodes regressed and were not enlarged on the short axis (Fig. 2A, B). The amount of fluid in the pericardium decreased.

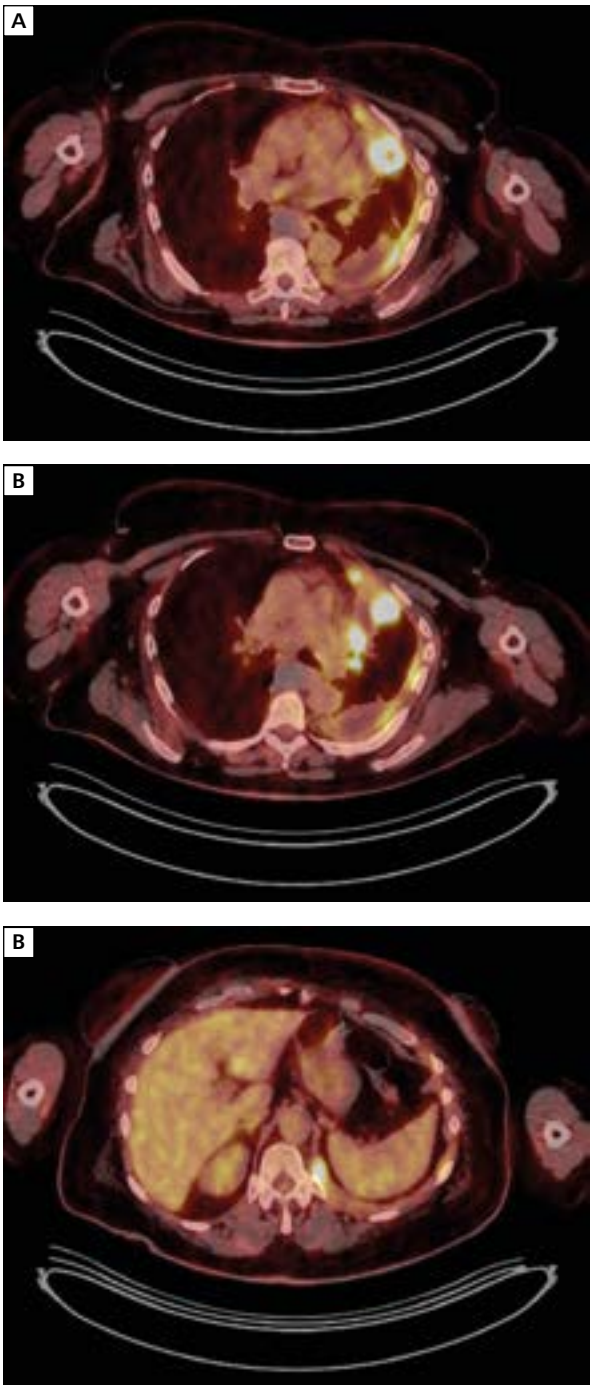

Figure 1. Positron emission tomography–computed tomography (PET-CT) images showing stage IV lung adenocarcinoma: primary tumor with dimensions of 33 × 32 mm (SUV_{max} 15.7 with a central cold area) and pleural effusion as well as metabolically active nodules in the left pleura (**A**); enlarged and metabolically active lymph nodes in mediastinum (**B**) and in the paraspinal region above the diaphragm (**C**)

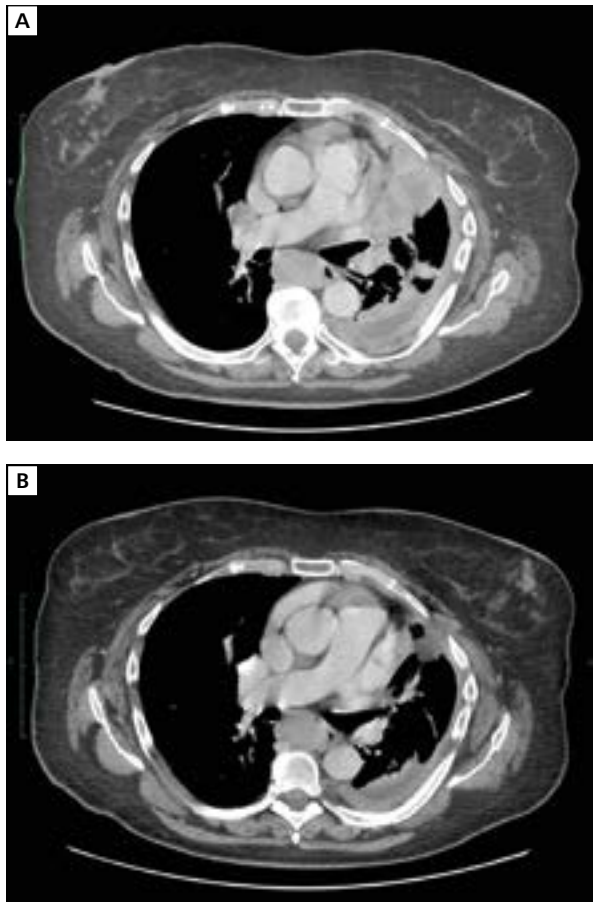

Figure 2. Computed tomography (CT) scans of November 15, 2021 (**A**) and February 3, 2022 (**B**) showing partial remission of the disease: reduction in the primary tumor dimensions, reduction of the pleural effusion and lack of enlarged mediastinal lymph nodes

After two months of treatment with alectinib, an increase in the activity of liver enzymes was noted — the increase in alanine transferase (ALT) values was 89 U/L, and asparagine transferase (AST) of 89 U/L [grade 1 toxicity according to Common Terminology Criteria for Adverse Events (CTCAE)] was detected. Alectinib therapy was continued with close observation. However, at the beginning of February 2022, grade 4 hepatotoxicity was found. The AST level increased to 905 U/L, the ALT level — to 732 U/L, and the bilirubin level — to 2 mg/dL. Alectinib therapy was interrupted until liver enzymes were normal. After 6 weeks, the patient received a reduced dose (300 mg twice a day) of alectinib, unfortunately, the activity of liver enzymes increased again. Alectinib therapy was permanently discontinued. After a significant decrease in liver enzymes in April (AST — 69 U/L, ALT — 58 U/L), brigatinib (another second-generation ALK inhibitor) was administered.

A different type of toxicity was observed after one month of brigatinib therapy at the standard dose (90 mg once a day for the first 7 days, then 180 mg once a day) in the form of an increased concentration of creatine kinase at 863 U/L. Brigatnib therapy was interrupted,

and after normalization of the enzyme concentration, the treatment was resumed at the same dose. After restarting treatment, the concentration of creatine kinase increased again to 1218 U/L. The enzyme concentration was rapidly normalized after withholding treatment. Currently, the patient continues brigatinib therapy at the reduced dose of 120 mg once a day. On subsequent follow-up CT, the disease remains stable (the size of the target lesion in the left lung is currently 21 × 11 mm).

Discussion

ALK gene rearrangement can be detected by IHC, FISH, and NGS. However, each of them has limitations. The gold standard was the FISH method, which was used in early clinical trials with crizotinib. It was validated during clinical trials of ALK inhibitors, but due to the costs and difficulties in interpretation of the results, FISH is increasingly replaced by other methods. The IHC method is not expensive and quite simple, which makes it useful in screening for the presence of abnormal ALK proteins. However, uncertain IHC results should be confirmed by FISH or NGS methods [3]. Mattsson et al. [4] studied 712 patients using both IHC (clone D5F3) and FISH methods. The FISH method detected ALK rearrangements in 13 patients and the IHC method in 14 patients. In 9 patients, the results from both methods coincided, however, in 5 patients the results were not confirmed. The study showed that sensitivity and specificity of the IHC method, compared to the FISH method, were 61.5% and 99.6%, respectively [4].

Currently, the NGS method is beginning to gain recognition because it allows detection of all fusion partners of the *ALK* gene. The most common fusion partner for the *ALK* gene is the *EML4* gene, however, there are several different variants of rearrangements. The other partners are the *KIF5B, KLC1, TFG,* and *PTPN3* genes. Not all diagnostic methods detect them all [3]. Siraj et al. examined patients using the NGS method. Of over a thousand patients, 47 were diagnosed with *ALK* gene rearrangements — in most patients (41 cases), the *EML4-ALK* fusion gene was detected while the remaining (6 cases) were *KIFB-ALK, CLTC-ALK, TFG-ALK, EIF2AK-ALK, PPM1B-ALK,* and *PRKAR1A-ALK*. Of these patients, 31 were also eligible for FISH and 11 of them had negative FISH test results. FISH failed to detect *EIF2AK3-ALK*, *PRKAR1A-ALK,* and one of the *EML4-ALK* variants [5]. In 2022, Zhao et al. [6] tested nearly 15000 patients using the NGS and IHC methods, including 12533 cases examined by DNA-based NGS and 2361 cases examined by RNA-based NGS tests. Based on DNA examination, they showed the presence of *ALK* gene rearrangements in 439 (3.5%) patients. RNA analysis identified fusion variants in 52 (2.2%) patients. At the same time, expression of ALK abnormal protein in the IHC test was detected in 455 patients from the DNA-tested group (3.6%) and 62 patients in the RNA-tested group (2.6%). Overall percentage agreement (OPA), positive percentage agreement (PPA), and negative percentage agreement (NPA) of NGS vs IHC test results were calculated. In the DNA-tested group, OPA, PPA, and NPA were 99.60%, 92.75%, and 99.86%, respectively. In the group of patients with adenocarcinoma, the PPA was 95.69%. Regarding the RNA-tested group, these values were as follows: 99.49%, 82.26%, and 99.96%, and in the group of patients with adenocarcinoma, the PPA was 82.26%. The percentage distribution of specific fusion partners was similar to the results of other studies. It is noteworthy that in one case where the *FAM114A1-ALK* variant was detected, it was not confirmed by any of the other methods (FISH, IHC, or RT-PCR) [6]. The results showed that only the NGS method could detect all partners of the *ALK* gene and all their variants, and perhaps in the future, it should become the gold standard in diagnosis of *ALK* gene rearrangement.

In the presented case report, *ALK* gene rearrangement was detected by the NGS and FISH methods. The IHC method failed to detect the abnormal ALK protein although the presence of the most common, first *EML4--ALK* fusion variant was confirmed. The fusion of exons 13 and 20 of these genes is not always the same. Exon 20 of the *ALK* gene contains 187 nucleotides. The most common exon 20 breakage points are known. However, DNA breakage could occur in different parts of exon 20. This influences the differences in the structure of the ALK protein, which may affect the effectiveness of IHC tests. Moreover, the ALK protein may be damaged during FFPE material formation. ALK protein expression may then not be visible in IHC assays. On the other hand, improper fixation of tissue material may damage DNA and RNA, which results in non-diagnostic FISH and NGS test results. In our patient, the results of genetic tests were diagnostic, which translated into the effectiveness of ALKi treatment.

Clinical response to ALKi might vary in *ALK* fusion subtypes, it can also change among different variants. Due to the limited number of rare fusion cases, it is difficult to compare the reasons for the differential responses of different rare fusions to ALKi and their resistance mechanisms [7].

The presented report describes the case of an NSCLC patient with *ALK* gene rearrangements treated with two different ALKi (alectinib followed by brigatinib) and various adverse events in the course of administering both medications. As first-line therapy, a highly selective, central nervous system-active drug — alectinib — was used. Alectinib is the second-generation ALKi, and it is characterized by good penetration of

the blood-brain barrier (BBB). Alectinib could achieve higher concentrations in cerebrospinal fluid (CSF) than a first-generation ALK inhibitor (crizotinib) [8]. A calculated CSF/plasma ratio in stable state is about 0.75 [9]. Indeed, good penetration to CSF seems to be a result of alectinib lipophilic properties [10]. Alectinib and its main active metabolite CH5468924000 (M4) showed high (more than 99%) binding to human plasma protein, however, protein-binding capacity did not depend on the concentration *in vitro* [11]. Moreover, in human studies, unchanged alectinib and M4 were found as major circulating moieties in plasma, where about 61% accounted for the parent compound. Similarly, both molecules were excreted primarily *via* the fecal route and unchanged alectinib contributed to 84% of administered dose [8]. The metabolism of alectinib is mostly mediated by hepatic cytochrome CYP3A, and gut metabolism seems to be negligible. M4 is developed as a result of demethylation at the morpholine ring *via* some intermediate metabolites, but predominantly M4 shows similar pharmacodynamic activity against ALK as a parent compound [10].

The mechanism of alectinib-induced hepatotoxicity remains unclear, however, studies on ALKi (including first-generation ALKi — crizotinib) in human hepatocyte cell lines suggest that mitochondrial failure and inhibition of glycolysis as well as reactive oxygen species (ROS) — dependent DNA damage may play an important role in liver failure caused by alectinib [12, 13].

Brigatinib is a second-generation, highly selective ALKi with a unique molecular structure and physiochemical features among the group of anti-ALK agents. In particular, such properties include a dimethylphosphine oxide (DMPO) group, attached to the C4 aniline substituent and a specific solubilization region connected to the phenyl ring at C2. DMPO group increases brigatinib activity against ALK, whereas the solubilization region is attributed to several pharmacokinetic properties such as low lipophilicity, low binding to human plasma protein (approx. 66%), and robust metabolic stability [14, 15]. When compared to alectinib, brigatinib shows apparent differences in excretion, for only 65% of the orally administered dose is found in feces, whereas 25% is eliminated via renal pathways. Metabolism of brigatinib is primarily mediated *via* CYP3A4 and CYP2C8, while N-demethylation and cysteine conjugation are found to be the main metabolic pathways. It is noteworthy that over 92% of the administered dose in plasma accounted for unchanged brigatinib and only 3.5% for primary active metabolite — AP26123. What is more, AP26123 showed about three-fold weaker activity against ALK than the parent compound [10].

Although structural and pharmacokinetic features of brigatinib are well described [14, 15], it remains unclear whether those differences may have any impact on the lower risk of brigatinib-induced hepatotoxicity in comparison with other ALKi [16]. Alterations in creatine kinase (CK) are recognized as common adverse events in patients treated with ALKi for solid tumors [17]. Based on a 2022 meta-analysis, the prevalence of brigatinib-induced CK elevation in NSCLC patients is approximately 30% [18]. CK is an essential enzyme for maintaining energy homeostasis, especially in tissues with high and floating energy requirements like cardiac and skeletal muscles. An elevation of CK may be assigned to concurrent inhibition of both ABL (*ABL* proto-oncogene) and AMP (Adenosine Monophosphate)-activated protein kinase (AMPK). In patients receiving ALKi therapy, skeletal muscle cells may share mutual tyrosine kinase metabolic pathways with NSCLC, and those pathways probably could be inhibited simultaneously [13]. Notably, there is some evidence that significant elevation of CK as a response to administered ALKi is connected with improved clinical efficacy and prolongation of survival [17, 19].

The introduction of ALKi into treatment significantly affected the quality and length of life of NSCLC patients with *ALK* gene rearrangement. In the ALEX study, superior effectiveness of alectinib over crizotinib was confirmed. Several side effects have been shown in patients treated with alectinib. Of the 79 patients who experienced serious adverse reactions (≥ 3 grade), 8 (5.3%) had an increase in AST and 7 (4.6%) in ALT activities, which in turn led to discontinuation of the drug [20]. For brigatinib, the ALTA clinical trial was the pivotal study. This study compared the effectiveness of brigatinib and crizotinib. Several adverse reactions have been observed in patients in association with the administration of brigatinib, the most commonly reported being an increase in CK concentration. There were 36 cases of this side effect, representing 20% of all patients [21]. Therefore, the toxicities that occurred in our patient were consistent with those observed in clinical trials conducted in patients treated with alectinib and brigatinib. Our approach to dose reduction or discontinuation of ALKi was also consistent with clinical trial results. However, managing toxicity by replacing one ALKi with another is unusual, and the decision must be made on an individual basis.

The ALEX and ALTA study demonstrated the efficacy of brigatinib and alectinib over crizotinib [20, 21]. However, there are several studies in which patients received brigatinib after chemotherapy or other ALK inhibitors, including alectinib, which demonstrated the efficacy of brigatinib over other second-generation inhibitors. Lin et al. [22] described 22 patients who were treated with brigatinib immediately after progression or toxicity during alectinib therapy. Of the 18 patients who had measurable disease, 3 had a partial response (PR)

and 9 had stable disease (SD). The mean PFS duration was 4.4 months, and the mean duration of treatment was 5.7 months. In addition, patients were re-biopsied after alectinib treatment and before brigatinib administration. Among 9 patients with detected resistance mutations such as G1202R, I1171N, I1171T, and V1180L, some achieved PR or SD during brigatinib therapy, which may indicate the effectiveness of brigatinib against tumor cells with some resistance mutations [22].

Nishio et al. [23] also studied *ALK*-rearranged NSCLC patients treated with alectinib. The studied group included 47 Japanese patients treated with first-line alectinib or alectinib after failure of crizotinib therapy. These patients, after progression on alectinib therapy, received brigatinib. The overall response rate to brigatinib therapy was 34%, and PR was achieved in 34% of patients, whereas SD was observed in 45% of patients. The duration of the response was 11.8 months. Resistance mutations after alectinib treatment were also detected among the subjects. The most common are G1202R, L1196M, I1171N, I1171S [23].

Popat et al. [24] observed brigatinib-treated patients who had previously been treated with ALK inhibitors, including alectinib. Of the 104 patients enrolled in the study, 93 benefited from brigatinib therapy. A complete response (CR) or PR was achieved in 37 patients (39.8%), and disease stabilization was obtained in 52 patients (55.9%). The mean PFS rate was 11.3 months, and mean overall survival (OS) was 23.3 months. More lines of treatment used before brigatinib therapy shortened both PFS and OS.

Conclusion

Our case report presents three difficult issues related to the diagnosis and treatment of NSCLC in patients with *ALK* gene rearrangement. First, the methods for *ALK* gene rearrangement diagnosis are not equally effective in some patients. It appears that NGS will become the preferred technique used for this purpose in the near future. Second, toxicities of different ALK inhibitors vary. Management of toxicity in patients with *ALK* gene rearrangement may include reduction of the ALKi dose or discontinuation of treatment, but also the replacement of inhibitors may be of value. Third, not only lorlatinib shows efficacy after second-generation of ALKi. It may be possible to continue successfully therapy if the second-generation ALKi is switched to a different one of the same generation due to toxicity.

Ethics statement

Not applicable.

Author contributions

M.G., P.K., M.S.: conceptualization; M.G., I.C., P.N., M.S.: resources; M.G., I.C., P.N., P.K., M.S.: writing — original draft preparation; P.K., M.S.: writing — review and editing; P.K., J.M.: supervision.

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Conflict of interest

Authors declare no conflict of interest.

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VIA MEDICA

CASE REPORT

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Efficacy of chemoimmunotherapy in a lung adenocarcinoma patient with mutations in the *KRAS* and *STK11*

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ABSTRACT

Immunotherapy is a groundbreaking treatment method when it comes to cancer, and this includes non-small-cell lung cancer (NSCLC). In NSCLC patients, immunotherapy is used in a form of immune checkpoint inhibitors (ICIs), and depending on the proportion of tumor cells with programmed death ligand 1 (PD-L1) expression on them, it can be administered either in monotherapy (≥ 50%) or in combination with chemotherapy (< 50%). In this article, we would like to present a case of a female patient with *Kirsten Rat Sarcoma Virus* (*KRAS*)-mutated lung adenocarcinoma who was responding to chemoimmunotherapy for a long time despite the presence of co-mutation in the *Serine/Threonine Kinase 11* (*STK11*) gene, known to worsen immunotherapy outcomes. In this patient, another mutation was found — in the *nibrin* (*NBN*) gene, which is of uncertain relevance, but it presumably could be connected to a better outcome as it encodes proteins involved in DNA repair. Deficiency in DNA repair may be marked by homologous recombination deficiency (HRD), and there already exists some evidence of better immunotherapy efficacy in patients with HRD. Considering the above, further investigation and thorough genetic diagnostics in NSCLC patients are required to fully understand the background of immunotherapy response.

Key words: chemotherapy, immunotherapy, lung adenocarcinoma, *KRAS* mutation, *NBN* mutation, *STK11* mutation

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Introduction

The KEYNOTE-024 study demonstrated the efficacy of pembrolizumab monotherapy in patients with programmed death ligand 1 (PD-L1) expression on more than 50% of tumor cells. However, later phase III clinical trials, KEYNOTE-189 and KEYNOTE-407, have proven the efficacy of pembrolizumab in combination with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC), regardless of PD-L1 expression on tumor cells [1]. Therefore, in routine clinical practice, chemoimmunotherapy is used in NSCLC patients with PD-L1 expression on fewer than 50% of tumor cells and after the exclusion of *Epidermal Growth Factor Receptor* (*EGFR*) gene mutations as well as *Anaplastic Lymphoma Kinase* (*ALK*) and *ROS Proto-Oncogene 1* (*ROS1*) genes rearrangements. In patients with adenocarcinoma, pembrolizumab in combination with platinum-based chemotherapy and pemetrexed is used. Maintenance therapy with pembrolizumab and pemetrexed might be continued after the end of the first phase of treatment. Currently, new therapeutic options have appeared for NSCLC patients with high (atezolizumab, cemiplimab) and low (atezolizumab in combination with chemotherapy and nivolumab plus ipilimumab in combination with limited chemotherapy) PD-L1 expression.

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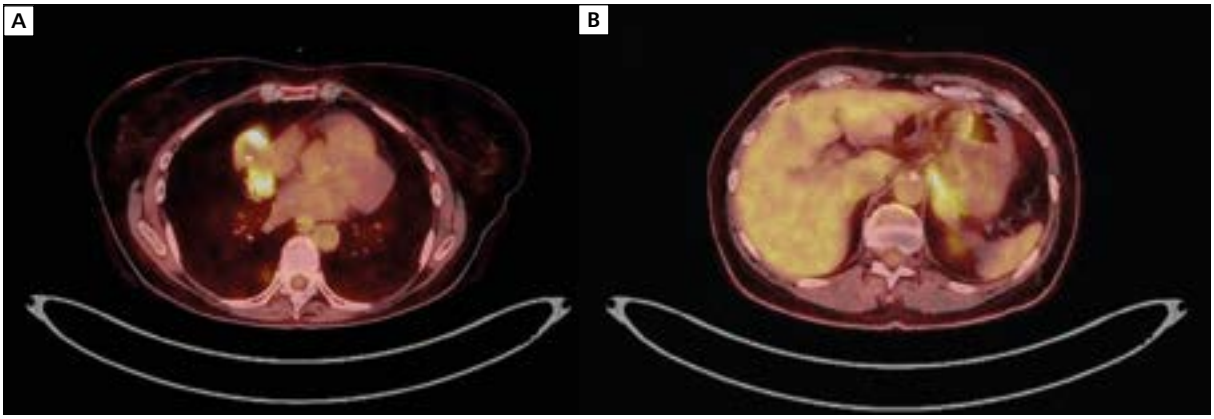

Figure 1. Positron emission tomography–computed tomography (PET-CT) scan images; **A.** An irregular nodal-infiltrative conglomerate in the right pulmonary hilum; **B.** Infiltration between the left adrenal gland and the stomach

The causes of primary and acquired resistance to immunotherapy and chemoimmunotherapy are not fully understood. It seems that they may be related to the molecular status of cancer cells. The presence of mutations in the *EGFR* gene, *ALK*, and *ROS1* gene rearrangements are associated with primary resistance to immunotherapy. These genetic abnormalities usually coexist with the low tumor mutation burden (TMB) in patients, which might be the cause of resistance. On the other hand, the presence of mutations in the *Kirsten Rat Sarcoma Virus* (*KRAS*) gene, which occurs mainly in smokers, may be associated with high TMB and response to immunotherapy. However, the coexistence of *KRAS* mutations and mutations in suppressor genes, such as *STK11* (*Serine/Threonine Kinase 11* also called *Liver Kinase B1*, *LKB1*), may result in the lack of response to immunotherapy. Contrarily, the coexistence of mutations in the *KRAS* and *TP53* (*tumor protein p53*) genes may increase the effectiveness of immunotherapy [2].

This case report concerns a patient with advanced adenocarcinoma of the lung who benefited from chemoimmunotherapy despite the coexistence of mutations in the *KRAS* gene with the loss of function of two tumor suppressor genes: *STK11* and *nibrin* (*NBN*). The patient gave his written consent to participate in the research based on the consent of the local bioethics committee at the Medical University of Lublin (No. KE-0254/160/2021).

Case report

A 69-year-old, non-smoking female patient reported to a pulmonology outpatient clinic due to a persistent dry cough. Chest X-ray, performed in June 2021, revealed infiltration in the area of the right lung hilum. The performance status of the patient was 1 according to the Eastern Cooperative Oncology Group (ECOG) scale. Hypertension, osteoporosis, and glaucoma were the only comorbidities. Family history included glioblastoma and salivary gland cancer diagnosed in the patient's mother.

In July 2021, a positron emission tomography–computed tomography (PET-CT) was performed. An irregular nodal-infiltrative conglomerate measuring 53 by 35 mm was found in the right pulmonary hilum. (^{18}F) 2-fluoro-2deoxy-D-glucose (^{18}F-FDG) accumulation was uneven and uttermost maximum standardized uptake value (SUV_{max}) was 11.45. In segment 10 of the right lung, a ground glass nodule of 14 mm and SUV_{max} value of 3.2 was visualized (Fig. 1A and 2A).

In addition, there was 45-mm-long infiltration between the left adrenal gland and the stomach with SUV_{max} 5.9 (Fig. 1B and 2C). The stage of the tumor was defined as c.T4N2M1 (stage IV).

Material for pathomorphological examination was collected during bronchoscopy with the endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA). Lung adenocarcinoma (LUAD) was diagnosed in July 2021. Analysis of the basic predictive factors showed no mutations in the *EGFR* gene, no rearrangements in the *ALK* and *ROS1* genes, and PD-L1 expression in 5% of the tumor cells. On this basis, the patient was qualified for chemotherapy with cisplatin and pemetrexed in combination with pembrolizumab immunotherapy based on KEYNOYE 189 study regimen. In the first control computed tomography (CT), partial response was achieved according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The infiltrative-nodal lesion in the left lung hilum decreased to 50 by 20 mm (Fig. 2B). The size of the ground glass nodule did not change. Complete remission was observed in the infiltrative lesion in the abdominal cavity (Fig. 2D). Partial response persisted, and it was

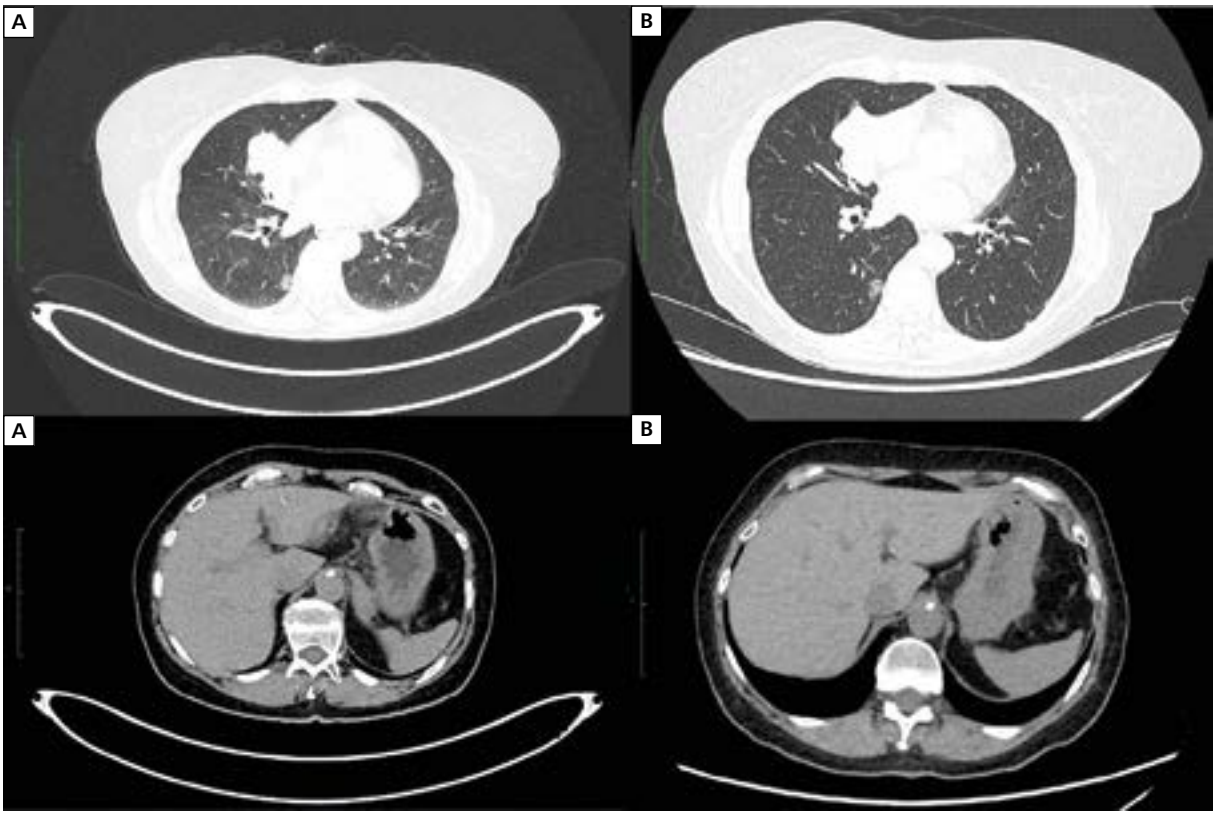

Figure 2. Computed tomography (CT) scan images; **A.** An irregular nodal-infiltrative conglomerate in the right pulmonary hilum; **B.** Partial response of the infiltrative-nodal lesion in the left lung hilum during immunotherapy; **C.** An infiltration between the left adrenal gland and the stomach; **D.** Complete remission of the infiltrative lesion in the abdominal cavity during immunotherapy

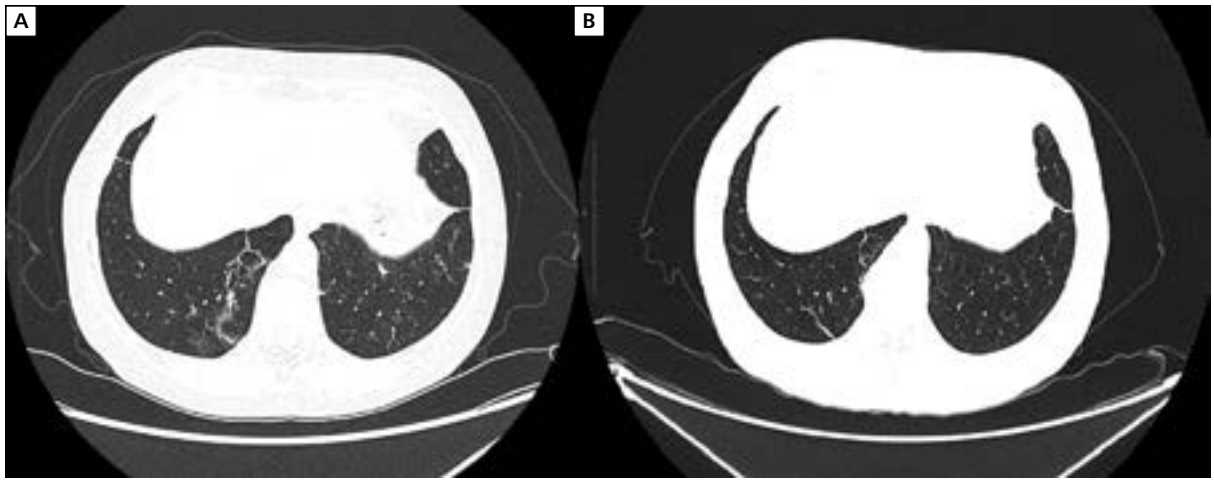

Figure 3. Computed tomography (CT) scan images; **A.** Inflammatory changes in the patient's lungs; **B.** Complete regression of inflammatory lesions

confirmed on subsequent CT scans during maintenance therapy with pemetrexed and pembrolizumab. The partial response continued (last observation in January 2023), resulting in progression-free survival (PFS) of 18 months. Chemotherapy and immunotherapy were very well tolerated.

In April 2022, a control tomography showed inflammatory changes (Fig. 3A) that could be associated with an oligosymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The complete regression of these lesions was observed on the next CT performed in July 2022 (Fig. 3B). Suspicion

of Coronavirus Disease 2019 (COVID-19) did not require discontinuation of pembrolizumab and pemetrexed therapy.

During therapy, the patient underwent next-generation sequencing (NGS) using FUNDATIONONE® CDx assay. Thereby, variants of known pathogenic status were identified in FFPE (Formalin-Fixed Paraffin-Embedded) material from the lung. First, there was a p.Gly12Val (p.G12V, c.35G>T) mutation in the *KRAS* oncogene (NM_004985). The second clinically significant mutation was p.Asp23fs*28 (p.D23fs*28, c.67delG) in the *STK11* gene (NM_000455). The third significant genetic alteration was p.Lys219fs*16 (p.K219fs*16, c.657_661delACAAA) in the *NBN* gene (NM_002485). TMB and microsatellite status in our patient could not be determined.

Discussion

KRAS, *STK11*, and *NBN* genes

The patient's tumor had pathogenic mutations in the *KRAS, STK11*, and *NBN* genes. The *KRAS* gene is a member of the RAS family of small guanosine triphosphatases (GTPases), and it is the most frequently mutated oncogenic driver in NSCLC, with the proportion of mutated patients at approximately 30%. *KRAS* gene mutations often occur with co-mutations and are associated with smoking [3]. There are few therapies intended for NSCLC patients with *KRAS* mutations as for a long time an appropriate drug could not be developed. Eventually, adagrasib (accelerated FDA approval) and sotorasib were registered for patients with the *KRAS* p.Gly12Cys (p.G12C, c.34G>T) mutation, which is the most frequent *KRAS* alteration in NSCLC [4–7].

Serine/threonine kinase 11 (*STK11*) gene encodes STK11 protein (also called LKB1), which is a kinase and acts as a regulator of apoptosis under stress, specifically energy deprivation, and it is considered a tumor suppressor [8]. In NSCLC patients, *STK11* mutations occur alone or, more frequently, as co-mutations with *KRAS* gene mutations. Approximately 8.6% of NSCLC patients without *KRAS* mutation and 25% of *KRAS*-mutated NSCLC patients are carriers of *STK11* mutations [3].

NBN gene encodes nibrin [also called Nijmegen Breakage Syndrome Protein 1 (NBS1)], a protein involved in double-strand DNA breaks (DSBs) recognition and repair. *NBN*-mutated patients suffer from Nijmegen breakage syndrome (NBS), which causes hypersensitivity to ionizing radiation and is characterized by chromosomal instability resulting in developmental disorders, immunodeficiency, and, notably, cancer predisposition [9]. Therefore, as nibrin is involved in homologous recombination (HR) and non-homologous end joining (NHEJ), the *NBN* gene may be assigned to a group of genes tested when homologous recombination (HR) deficiency (HRD) is assessed [10, 11]. *NBN* mutations are relatively rare in NSCLC patients (< 3%), with the frequency of p.K219fs mutation at 0.16%, and there is no targeted therapy for cancer patients with alterations in this gene. The mutation p.K219fs in the *NBN* gene resulted in the lack of expression of this gene in cancer cells [12, 13]. The presence of this mutation in our patient may explain the occurrence of cancer in her family. However, the presence of a mutation in the *NBN* gene had not been tested in our patient's peripheral blood, and this mutation may only be present in cancer cells [somatic mutation according to the Catalogue of Somatic Mutations in Cancer (COSMIC)].

The efficacy of immunotherapy and chemoimmunotherapy in *KRAS*-, *STK11*-, and *NBN*-mutated NSCLC patients

Due to a lack of KRAS-targeted therapy for lung cancer patients, immunotherapy has been commonly used. In general, immune checkpoint inhibitors (ICIs) are effective in this group of patients, but the response depends on the presence of co-mutations, and patients with *STK11* co-mutations have shorter survival and lower response rates than those with *TP53* co-mutations or even those with *KRAS*-mutated *STK11*-wild type. In one of the studies examining ICI effectiveness in NSCLC patients, the overall response rate (ORR) in a *KRAS*- and *STK11*-mutated subgroup was 7.4%, whereas, in a group with *KRAS* and *TP53* mutations, the ORR reached 35.7%. In clinical trials, a combinatorial approach is being investigated. KRAS inhibitors are administered with ICIs in ongoing clinical trials (sotorasib in the CodeBreaK 101 study, and adagrasib in the KRYSTAL-7 study, both in patients with *KRAS* G12C mutation). Differences in response are probably related to tumor microenvironment (TME) characteristics that are diverse, depending on the alterations occurring. *STK11*-mutated tumors exhibit lower lymphocyte infiltration and lower PD-L1 expression, compared to *TP53*-mutated ones [2].

NBN is one of the proteins involved in the HR mechanism, and HRD sensitizes tumors to poly ADP-ribose polymerase (PARP) inhibitors and platinum-based chemotherapy, but little is known about the predisposition to immunotherapy [14, 15]. A study by Yang et al. [16] included ICI-treated patients (an independent breast cancer cohort), and 11 *in vivo* murine mammary tumor models treated with anti-PD-1/anti-CTLA-4 antibodies. In many cancer types, including LUAD and squamous lung cancer, a high HRD

score was connected to neoantigenesis and a TME well-infiltrated by lymphocytes. Such features indicate that cancer cells may be easily detected, accessible to T cells, and eventually destroyed. Guo et al. [17] conducted an analysis on thousands of patients with 9 types of cancer (including NSCLC). They described that mutations in 7 DNA repair genes, including *NBN* (*ATM*, *ATR*, *POLE*, *ERCC4*, *NBN*, *RAD50*, *PARP1*), were associated with improved overall survival (OS) in patients treated with ICIs ($p < 0.05$ for all genes). Mutations in genes whose products are involved in HR were not associated with worse OS in patients without ICI treatment [17]. Hsiehchen et al. [18] similarly revealed a positive correlation between HR gene mutations (NGS analysis) and OS in ICI-treated patients independently of TMB. *NBN* gene mutations were included in the sequencing procedure. Median OS (mOS) was 41 months in patients with HR gene mutation *vs.* 16 months in patients without these mutations ($p < 0.001$). Additionally, the authors stated that objective response was more frequently present in patients with mutations in genes involved in HR and NER (nucleotide excision repair) DNA repair mechanisms ($p = 0.041$ for the NSCLC cohort) [18]. Zhou et al. [19] tested ICI therapy in a neoadjuvant regimen in a small cohort of NSCLC patients (13 of them received chemoimmunotherapy with a PD-1 inhibitor, and 1 patient received anti-PD-1 with anti-CTLA-4 immunotherapy). Among those patients, 3 had a major pathological response (MPR), and 3 had a complete pathological response. In patients with MPR, mutations in genes involved in the HR process were enriched, and these findings were then confirmed in public cohorts [19]. In contrast, Kim et al. [20] analysis did not demonstrate that HRD is an effective predictive marker for ICIs in solid tumors, but this study did not include NSCLC patients. Moreover, HRD or HRD scores are often estimated in different ways and thus, studies determining the most efficient method are necessary to verify HRD predictive value.

Several questions still need to be answered. Parkes et al. [21] provide a possible explanation for enhanced anti-tumor response in patients with mutations in DNA damage response (DDR) genes. They have observed that PD-L1 expression ($\geq 1\%$ or $\geq 5\%$) in samples from DDR-deficient breast tumor patients was positively associated with DDR deficiency assay positivity ($p < 0.001$ for both cut-offs). They have also stated that the activation of the innate immune Stimulator of Interferon Genes (STING)-mediated pathway is responsible for chemokine production in response to DNA damage *in vitro*, resulting in an inflammatory TME in DDR deficient breast tumors [21]. This, combined with enhanced PD-L1 expression in those patients and increased neoantigen expression, may lead to stronger immune system activation and anti-tumor response. Assumably, combining PARP inhibitors and immunotherapy would be a way to intensify this effect. Such a strategy is being investigated in some patients, and Xu et al. [22] described a case of *ROS1*- and *NBN*-mutated patient with long-term response to an ICI — sintilimab (anti-PD-1 antibody) in combination with PARP inhibitor — niraparib after the failure of ROS1 inhibitor therapy.

Conclusions

To conclude, the reported patient with several mutations had a slightly complex genetic background of response to chemoimmunotherapy. Although most of the studies are limited and retrospective, there is some evidence regarding immunotherapy efficacy in NSCLC patients with such mutations. While *KRAS* and *NBN* mutations seem to be favorable, *STK11* alterations are associated with poor immunotherapy outcomes. Additionally, *NBN* mutations are (as the *NBN* gene products are the member of the HR pathway) predictors of good response to platinum-based chemotherapy, which the patient was receiving. HRD is certainly worth considering in terms of immunotherapy outcome prediction, but it requires a standardization process. It is clear that we do not fully understand the immunological and genetic grounds of anti-cancer therapies' effectiveness, and thorough research is crucial to qualify patients properly for treatment.

Ethics statement

The patient gave his written consent to participate in the research based on the consent of the local bioethics committee at the Medical University of Lublin (No. KE-0254/160/2021).

Author contributions

N.K.: article concept, writing, clinical data collection, literature data collection; P.K.: article concept, revising the article; I.C.: clinical data collection; T.J.: clinical data collection; K.W.-K.: writing, and supervising the article; J.M.: revising the article.

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

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Conflicts of interest

Authors declare no conflict of interest.

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Hypopituitarism as a rare complication of lung cancer immunotherapy

Key words: hypopituitarism, cancer immunotherapy, pembrolizumab, lung cancer

Although hypopituitarism is a rare complication of cancer immunotherapy (occurs in 0.1–2.4% of patients depending on publication and use of monoclonal antibodies), nowadays immunotherapeutic agents are the main notable cause of hypophysitis [1, 2]. We present a case of hypopituitarism in a patient with non-small cell lung cancer (NSCLC) treated with pembrolizumab.

A 62-year-old male patient was admitted to the Ward of Clinical Oncology to be qualified for systematic therapy. In the past, the patient underwent cardiological and cardiosurgical interventions, including coronary artery bypass, due to myocardial infarction (2 years before qualification for immunotherapy; under the supervision of a cardiac center). The histopathological result revealed squamous cell carcinoma (SCC) of the left lung (T3N0M0). The expression of programmed death ligand 1 (PD-1L) was estimated to be 70%. Until then the patient was treated by radiotherapy without therapeutic success because of developing metastases to the second lung, suprarenal gland and bones. The laboratory tests (Tab. 1) and CT scans were ordered. The features of prior myocardial infarction were the only findings on ECG. The Concilium qualified the patient for immunotherapy in a regime of 200 mg of pembrolizumab every 21 days.

Table 1. The results of patient's blood test before and after administration of prednisone

	Before treatment	After treatment	Reference range
Corticotropic axis			
ACTH [pg/mL]	< 1	54.28	7.20–63.60
Cortisole [μg/dL]	3.70	10.20	4.30–22.40
Thyrotropic axis			
TSH [mIU/L]	0.117	2.454	0.550–4.780
fT4 [ng/dL]	0.81		0.89–1.76
fT3 [pg/mL]	2.50		2.30–4.20
Inflammation markers			
CRP [mg/L]	179.127	162.459	< 5.00
WBC [K/μL]	21.47	13.75	[4.00–10.00]

ACTH — adrenocorticotropic hormone; CRP — C-reactive protein; fT3 — free triiodothyronine; fT4 — free thyronine; TSH — thyrotropic hormone; WBC — white blood cells.

According to RECIST 1.1 criteria, the patient's status after the first month was stable disease (SD). The change in the sum of measurable diameters of 2 included lesions was estimated to be 85%. When the patient was admitted to the ward to have the sixth cycle of therapy

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administered, he reported a group of symptoms suggesting hypopituitarism (weakness, drowsiness, low blood pressure). According to the clinical picture, hormonal tests were done (Tab. 1).The insufficiency in corticotropic and thyrotropic axes was reported, which led up to endocrinological consultation. The consulting physician suspected immunotherapy-related hypophysitis and recommended prednisone (1 mg/kg) per os, with further hospitalization in the Endocrinology Clinic [to do magnetic resonance imaging (MRI) of the hypothalamic-pituitary region and further diagnostics]. A decision on the substitution of thyroid hormones was temporarily delayed and later withdrawn due to improvement in the patient's condition and laboratory results.

On steroid therapy, the patient's condition improved, and normalization in corticotropic and thyrotropic axes followed. The patient opted for hospital discharge with prednisone; immunotherapy was temporarily stopped. The patient died at home from a suspected cardiovascular event 2 days later.

The effectiveness of prednisone in oncological patients with hypopituitarism as an immunotherapy complication remains inconclusive according to the available literature [1, 2]. On the other hand, prednisone is currently recommended by the European Society for Medical Oncology (ESMO) guidelines for immunotherapy-related hypophysitis treatment [3]. The long-term complications (iatrogenic Cushing syndrome) are indicated as a main high-risk disadvantage of intense steroid therapy, none of which correspond with the presented case.

Author contributions

J.K.G.: data collection, data analysis, manuscript writing; A.R.: data collection, data analysis, manuscript writing; G.R.: data collection, data analysis, protocol/project development, manuscript writing; K.Sz.: protocol/project development, data collection and management; S.M.: manuscript writing and editing.

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Conflict of interest

Authors declare no conflict of interest.

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