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Novel immunotherapy in the management of advanced urothelial cancer- review of the literature

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Abstract:

Bladder neoplasms, with the most common urothelial carcinoma, are responsible for approximately 200,000 deaths annually, which is 2.1% of the total cancer deaths in 2018. Recent decades have brought a steadily growing share of this cancer in the statistics. The 5-year survival rate is 77.1% for the United States and it varies depending on the stage of the diagnosed neoplasm, from 96% for cancer in situ to only 5% for the disseminated form with distant metastases. The treatment of urothelial cancer can be divided depending on the stage and advancement. Three main categories of bladder cancer can be distinguished: non-muscle invasive bladder cancer, treated by surgical approaches, and muscle-invasive bladder cancer, treated with chemotherapeutics, lastly advanced bladder cancer with distant metastases, treated with intensive chemotherapy in the MVAC scheme (methotrexate, vinblastine, doxorubicin, and cisplatin). Recently introduced checkpoint inhibitors have revolutionized the treatment of patients with metastatic urothelial carcinoma by increasing patient life expectancy, progression-free survival, and durability of clinical response. This review of the literature will discuss the use of immunotherapy in the treatment of advanced bladder cancer.

Keywords: bladder cancer; urothelial carcinoma; immunotherapy; checkpoints inhibitors

Introduction:

In 2020, GLOBOCAN reported 19,3 million new cancer cases diagnosed worldwide. Among the statistics, bladder cancer (BC) is the 10th most often diagnosed malignancy and is responsible for over half a million cases and two hundred thousand deaths(1). In Poland, it is prevalent in 6.7% of cases in men and 2% of cases in women(2). However, there has been a downward trend in the incidence of BC over the last 40 years (3). The most common BC is urothelial carcinoma, cancer derived from the transitional epithelium of the urinary tract which appears in 90% of cases (3). The remaining 10% consists of squamous cell carcinoma accounting for 5% and other tumors, including sarcomas and metastases of other neoplasms, accounting for 5% (3). Incidence is the highest in European countries, the United States, North African countries, and the Middle East (4). In African countries, squamous cell carcinoma of the bladder, linked with the carcinogenic effect of schistosomes, is prevalent (5–7). Smoking is considered to be the main risk factor, which accounts for 50-65% of cases (3). Other risk factors include exposure to aromatic hydrocarbons, coal dust, long-term consumption of water contaminated with arsenic or chlorine, exposure to ionizing radiation, and a family history of bladder cancer (8). Also, as novel studies show, the use of pioglitazone slightly increases the risk of developing bladder cancer, hypothetically responsible for 5 out of 100,000 cases (9). Diabetes mellitus is a documented risk factor only in men, its duration is also negatively correlated with the risk (10). In North African countries, *Schistosoma haematobium* infection is considered the main risk factor for the development of bladder cancer (11). Considering the incidence of urothelial cancer in developed countries, a conclusion was drawn about the correlation with the toxins present in the environment, mainly the aforementioned aromatic amines and 4,4'-methylenebis(2-chloroaniline) found in both tobacco smoke and hair dyes, paints, and fungicides, among others (3). BC is a great medical and economic problem in highly developed countries. However, a focus on immunotherapy treatment has allowed to extend patients' lives and reduce mortality in recent years (1).

Bladder cancer classification and pathophysiology :

The staging of bladder cancer is based on a histopathological assessment of the presence and degree of infiltration of the bladder wall. The clinical division, on which further therapeutic management depends, divides bladder cancers into non-invasive - nMIBC (non muscle invasive bladder cancer) and infiltrating - MIBC (muscle-invasive bladder cancer) (12). However, bladder cancer is a very heterogeneous disease entity, and different tumors can be part of both MIBC and nMIBC (13). In recent years, two pathways of carcinogenesis have been formulated, separate for MIBC, whose precursor seems to be dysplasia of the urinary tract epithelium, and for NMIBC, whose precursor change is hyperplasia in the epithelium (14). Non-infiltrating cancer accounts for over 70% of new diagnoses (15). Both types, like most cancers, are based on changes in the genetic code of cells. Recently, targeted therapies and immunotherapy have become breakthroughs, based on detailed studies of the genetic basis of cancer. Therefore, there is such a great and pressing need for a thorough examination and qualification of the pathological basis of bladder neoplasms. Looking at the disorders of the genome of neoplastic cells, we distinguish between low-risk and high-risk cancers, low-grade cancers are distinguished by genome and mutation stability, while high-grade genome instability and numerous changes predisposing malignancy are distinguished (16). In low-grade tumors, the

basic genome change turns out to be FGFR3 gene mutations and epithelial hyperplasia, while in high-grade tumors, TP53 changes and epithelial dysplasia, which gives a dualistic division and directly affects the targeting of therapy depending on the pathological characteristics of the tumor (17). The studies distinguished six molecular subtypes of invasive bladder cancer: luminal papillary, luminal specified, luminal unstable, stroma-rich, basal/squamous, and neuroendocrine-like. Due to the histological picture, urothelial carcinoma is a very heterogeneous group, basic immunohistochemical staining allows for the distinction of the luminal phenotype and the basal cell phenotype, other phenotypes include conventional urothelial carcinomas, microtuberosomas, plasmocytoid and nested variants of urothelial carcinomas (14). There is a relationship between molecular subtypes and histological phenotypes which translate into the treatment of a given tumor type (18).

Overview of the bladder cancer treatment:

The treatment of urothelial cancer depends mainly on its clinical stage, thus the decision between surgical treatment and pharmacological therapy is based on the type of neoplasm. The risk of relapse and disease progression can be estimated for individual patients using the European Organization for Research and Treatment of Cancer (EORTC) scoring system (19). The categorization of patients into low, medium, and high risk groups is key to the use of adjuvant therapy. In patients with tumors considered to be low-risk neoplasms and in patients considered to be in the intermediate-risk group, with a low rate of previous relapses and the predicted number of relapses on the EORTC scale <5, it is recommended to administer chemotherapy once as soon as possible (12). In clinical trials, the effectiveness of an immediate single intravesical infusion - SI (single installation), which is responsible for the destruction of residual cells and lesions not removed during TURBT, has been demonstrated. The most favorable effect of SI occurs with the use of mitomycin C (MMC) and epirubicin (20). Patients with intermediate-risk tumors should receive a full dose of intravesical immunotherapy - BCG for one year or chemotherapy for up to one year. In patients with high-risk neoplasms, full-dose intravesical BCG therapy is indicated for 1-3 years. Immediate radical cystectomy should be considered in patients at the highest risk of tumor progression. Cystectomy is recommended in tumors that do not respond to BCG (12). MIBC usually requires radical cystectomy with resection of regional lymph nodes (21). Non-surgical treatment is possible, but it is significantly more challenging with much greater involvement of both a multidisciplinary team of specialists and the patient (22). Although the proper resection, the risk of recurrence and metastasis in patients with MIBC is around 50% due to the presence of micrometastases in the surrounding tissues (23). This urges the need to add supplementary therapies in advanced forms of this cancer. In the case of MIBC, neoadjuvant therapy with the use of cisplatin reduces the risk of recurrence and increases survival compared to surgical treatment alone (24). Cisplatin-based therapies are typically based on dd-MVAC (dose-dense methotrexate, vinblastine, doxorubicin, cisplatin) or GC (gemcitabine, cisplatin) regimens (12,24). About 50% of patients with advanced bladder cancer cannot take cisplatin, mainly due to its high toxicity (25). In the case of contraindications to the use of cisplatin-based therapy, most often caused by renal failure, carboplatin regimens are used, which show slightly worse effectiveness of the clinical response (26). Patients diagnosed with metastatic BC should receive chemotherapeutic-based treatment as a standard (27). Advanced urothelial carcinoma is considered an incurable disease and the only currently available option for the affected patients is palliative care (28). The current state

of knowledge supports the use of chemotherapy in advanced/metastatic disease, providing reliable symptom relief and a median survival ranging from 13 to 18 months (21). Currently, according to the guidelines of the European Urological Association, ECOG-assessed patients with metastatic disease should be treated with cisplatin-based chemotherapy. Patients ineligible for cisplatin should receive immunotherapy (PD-L1 positive patients) or carboplatin (PD-L1 negative patients).

Immunotherapy in bladder cancer:

Urothelial carcinoma shows high levels of PD-L1 (programmed cell death ligand 1 protein) expression, suggesting tumor-related immune tolerance and escape of tumor cells from immune surveillance (29). Expression of PD-L1 was noted in approximately 20% of the tested tumor tissue samples (30). PD-1 and PD-L1 inhibitors are used in the treatment of advanced stages of urothelial cancer (12). Five substances with this mechanism of action are approved for use by the FDA (Food and Drug Administration): atezolizumab, pembrolizumab, nivolumab, avelumab, and durvalumab (29). Immunotherapy is initiated in patients who have progressed after treatment with cisplatin or carboplatin and who have not received prior immunotherapy. The use of atezolizumab as first-line therapy in patients who cannot or cannot tolerate cisplatin as first-line therapy has been a breakthrough (31).

Atezolizumab:

Atezolizumab was the first immunotherapeutic agent approved for the treatment of advanced urothelial cancer. The 2016 phase III study, IMvigor130, aims to compare the treatment with atezolizumab in combination with chemotherapy and chemotherapy alone in metastatic urothelial cancer. The study included patients who met the eligibility criteria for treatment with platinum derivatives. The primary endpoints of this study included median overall survival (OS), progression free survival (PFS), and percentage of participants with adverse events (AEs) (32). Patients were randomized into 3 groups: atezolizumab in combination with platinum-based chemotherapy (Group A), atezolizumab as monotherapy (Group B), or placebo plus platinum-based chemotherapy (Group C). Patients were followed for 11.8 months. PFS for group A was 8.2 months, while for group C it was 6.3 months ($p = 0.007$, HR = 95%). The OS for group A was 16 months, and for group C it was 13.4 months. AE in group A was 34%, and in group C an identical result of 34% was achieved (32). No additional side effects were observed as compared to monotherapy. The safety profile of therapy with PD-1 / PD-L1 inhibitors was comparable to that of platinum-based chemotherapy. The use of monotherapy with atezolizumab was approved in 2017 by the FDA for patients with metastatic urothelial carcinoma in the case of existing contraindications to the use of platinum derivatives (33). These results support the use of atezolizumab in combination with platinum-based chemotherapy as an effective first-line therapy in metastatic urothelial carcinoma. The efficacy and safety of monotherapy with atezolizumab as first-line treatment in patients with metastatic urothelial carcinoma, observed in a previous Phase 2 study (2017 IMvigor210) limited to patients eligible for cisplatin treatment, were also repeated in the IMvigor130 study in more patients (34).

Nivolumab:

Nivolumab is a human IgG4 monoclonal antibody directed against PD-1 receptors. It is used in therapies aimed at reducing the size of the tumor in inoperable urothelial carcinoma and the advanced stage of this tumor with metastases (29). The efficacy of nivolumab was studied in the 2017 phase II clinical trial CheckMate-275 with a minimum follow-up of 7 months, the objective response rate (ORR) was 19.6% using the RECIST criteria (Response Evaluation Criteria in Solid Tumors) 1.1. The median duration of response (DOR) was not reached, median PFS using RECIST 1.1 was 2.0 months and median OS was 8.7 months (29,35). The study showed high efficacy in patients with disease progression after previous platinum therapy (35). Treatment-related adverse events occurred in 64% of patients. The most common treatment-related adverse reaction was fatigue (17%). Diarrhea (2%) was one of the less common side effects of nivolumab therapy (30). In a follow-up study conducted 3 years after the publication of the results of the CheckMate275 study, it was confirmed that nivolumab monotherapy provides a permanent protective effect against tumor progression in patients with inoperable urothelial carcinoma or neoplasms resistant to platinum-based therapy (mUC) (35). Additionally, during the long period of observation of patients after the applied treatment, no new adverse effects of the therapy were observed (35).

Pembrolizumab:

Humanized IgG4 monoclonal antibody directed against the PD-1 molecule, currently used in the treatment of melanoma, PD-L1 positive lung cancer, and in relapse and/or metastasis of squamous cell carcinoma, after progression or during platinum chemotherapy (36).

In a 2017 phase 3 trial, KEYNOTE-045, pembrolizumab was compared with paclitaxel, docetaxel, or vinflunine (37). The study included patients with metastatic or locally advanced/inoperable urothelial carcinoma who had relapsed or progressed after platinum-based chemotherapy (37). The primary endpoint was OS and PFS as measured by RECIST 1.1 over 20 months comparing both treatment strategies (37). OS and PFS in the study were assessed by groups, in all subjects, for strong PD-L1 positive tumors (expressing greater than or equal to 10% PD-L1) and PD-L1 positive tumors (expressing greater than or equal to 1% PD-L1). PFS according to RECIST 1.1 was 2.1 months, compared to the control trial which achieved a PFS of 3.3 months (37). The OS with pembrolizumab administration was 10.3 months, while in the control trial it was 7.4 months (37). The ORR was 20.3% in the study group, and 6.7% in the control group (37). ORR in the group of participants with PD-L1 positive tumors was 22.7 in the study group and 8.7 in the control group (37). There were no more side effects of pembrolizumab compared to the use of chemotherapy (37). The results show the advantage of using pembrolizumab over chemotherapy in all study groups concerning the OS results. There were no statistically significant differences in PFS between the treatments used. Also, AEs were significantly more frequent in patients receiving chemotherapy compared with patients receiving immunotherapy (37). Among the patients treated with pembrolizumab, pneumonia, enteritis, and urinary tract infections were the most problematic. It can therefore be concluded that pembrolizumab extends the life of patients with advanced urothelial cancer.

Durvalumab:

Immune checkpoint inhibitors, as well as others, target the interaction of PD-1 molecules with PD-L1. 2021 brought the results of phase III clinical trial of MEDI4736 in combination with tremelimumab (human anti-CTLA-4 antibody) or without it compared to standard chemotherapy (cisplatin with gemcitabine or carboplatin with gemcitabine, depending on cisplatin qualification) – DANUBE (38). Eligible patients had to meet the criteria for diagnosis (histology or cytology) of inoperable stage IV urothelial carcinoma, without prior treatment with first-line chemotherapy, or ineligible for cisplatin-based chemotherapy. Patients enrolled in the study had to have documented positive PD-L1 status. Patients were followed up for 2 years, and the primary endpoints were the efficacy of durvalumab and tremelimumab combination therapy versus chemotherapy based on OS, and the evaluation of durvalumab monotherapy versus chemotherapy in patients with high PD-L1 expression. OS in the studied group of PD-L1 patients treated with durvalumab monotherapy compared to chemotherapy was 14.4 months for durvalumab and 12.1 months for chemotherapy, hence we can state no statistically significant difference between the results (38). Serious adverse events concerned mainly the group treated with chemotherapy - 60%, including anemia, fever, urinary tract infections, two deaths related to the treatment were reported among intervention patients, while in the control group only one (38).

Avelumab:

Avelumab is a human IgG1 monoclonal antibody directed against PD-L1. The JAVELIN Bladder 100 study allowed the FDA to qualify this agent for the treatment of advanced urothelial cancer (39). Therapy included patients who, despite treatment with platinum-based chemotherapy, did not show a response, also as a maintenance treatment after treatment with platinum derivatives under the influence, which stabilized the neoplastic process (22). The study enrolled patients with stage IV cancer at the start of treatment who had received a minimum of 4 cycles but not more than 6 cycles of gemcitabine plus cisplatin and/or gemcitabine plus carboplatin. It was also necessary to determine the lack of disease progression after first-line chemotherapy. JAVELIN 100 compared the treatment with avelumab and the best supportive care including antibiotic therapy, nutritional treatment, and correction of metabolic disorders. The primary endpoint was OS, secondary endpoints include PFS and OR. The OS of patients treated with avelumab was 21.4 months, while in the control group it was 14.3 months (22). PFS was 3.7 months for patients treated with avelumab and 2.0 for the control trial (22). The JAVELIN study revealed a significant extension of the life of patients with advanced urothelial carcinoma with relatively low side effects of the therapy (22,31).

Conclusion:

Recent years have brought a breakthrough in the treatment of urothelial cancer and many other advanced neoplasms. Chemotherapy based on platinum derivatives has remained the standard of treatment for urothelial cancer since the 1970s, but we are currently experiencing a new era of treatment based on immunotherapy. Even though the first drug in this indication is

atezolizumab, studies have allowed the introduction of other immunotherapeutic preparations into the therapy. The promising results of studies on nivolumab or pembrolizumab allow us to boldly state that both of these preparations will significantly improve the treatment outcomes of patients with advanced urothelial cancer in the future. Each nivolumab and pembrolizumab, durvalumab, and avelumab have been approved by the FDA for the treatment of advanced urothelial cancer, which is unresponsive to platinum derivatives. Due to the promising results, pembrolizumab has also been approved for the treatment of urothelial carcinoma in situ. This illustrates the high hopes for relatively safe and less burdensome treatment of tumors with a significant advancement. A surprising and future-oriented solution indicating the priority of further studies is to allow the use of atezolizumab in this indication, even without PD-L1 determination, although the expression of these receptors significantly influences the patient's response to treatment, as shown in all studies available to us. Immunotherapy also offers prospects for patients disqualified from platinum chemotherapy, including patients with kidney injury, patients with audiometric hearing loss, peripheral neuropathy, and New York Heart Association (NYHA) heart failure greater than or equal to class III. Despite the progress in current treatment, trials on small groups of patients show a clear need to investigate the optimal method of treatment with these substances, including the sequence, duration of treatment, or combination of preparations with each other and drugs with different target points. We still lack unambiguous answers for patients with relapses or progressing patients despite intensive immunotherapy and chemotherapy. All these impressive research results have created a solid foundation for the further development of immunotherapy, which has shown hope for many patients with advanced urothelial carcinoma in recent years.

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