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REVIEW ARTICLE

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Maintenance avelumab in metastatic urothelial cancer patients

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ABSTRACT

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

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

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Introduction

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

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

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

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

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Maintenance treatment

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

Maintenance treatment in patients with metastatic urothelial carcinoma

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

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

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

Avelumab treatment for metastatic urothelial carcinoma

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

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

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

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

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

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

Summary

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

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

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

Conflict of interest

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

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