



Immunotherapy for advanced urothelial carcinoma (UC): rational and current evidence[✱]

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Abstract: Combination platinum-based chemotherapy has been the standard of care for several decades in first-line treatment of advanced urothelial carcinoma (UC) patients. UC is often chemosensitive, though durable responses are quite rare and the development of chemoresistance still leads to poor clinical outcomes. Up until a few years ago, UC patients could not benefit from any valuable alternatives to cytotoxic chemotherapy, but the scenario has been recently transformed by the advent of immunotherapy. Molecular biology of UC is characterised by a relatively high prevalence of alterations in DNA damage response pathway, genomic instability, high tumour burden, and elevated programmed cell death ligand 1 (PD-L1) protein expression, which are established factors predicting favourable response to immune checkpoint inhibitors (ICIs) in several tumour types. To date, various ICIs have been approved as systemic anti-cancer therapy for advanced UC in multiple settings, including first-line, maintenance, and second-line therapy. ICIs are also in development either as monotherapy or in combination with chemotherapy or other targeted agents. Moreover, a number of alternative ICIs, interleukins, and novel immune molecules have been identified as promising agents in advanced UC. Herein, we review rational and current literature evidence supporting the clinical development and current indications of immunotherapy, particularly focusing on ICIs.

Keywords: Urothelial carcinoma; bladder cancer; immunotherapy; immune checkpoint inhibitors (ICIs)

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Introduction

Background

The chemotherapeutic management of patients with advanced urothelial carcinoma (UC) has changed little over the last 20 years. Platinum-based doublets remain the standard of care in the first-line setting. Although chemotherapy has relatively high level of activity, most patients will ultimately progress within 9 months of therapy, with median survival slightly exceeding 12 months with cisplatin-based combinations. Shorter survival of around 9 to 10 months has been reported in cisplatin-ineligible subjects treated with carboplatin-based chemotherapy (1,2). The underlying mechanisms of platinum resistance are multifactorial and complex, involving expression of molecules involved in cisplatin transport and detoxification, increased DNA repair, and reduced apoptosis (3). Single agent taxanes or vinflunine have exhibited modest clinical activity and were previously the standard salvage systemic therapy in advanced UC (4). In the era of precision medicine, multiple targeted therapies have been successfully evaluated in advanced UC. Following the results of the phase 3 EV-301 trial, the antibody drug conjugate enfortumab vedotin has been approved for advanced UC patients who received a prior platinum-containing chemotherapy and an immune checkpoint inhibitor (ICI) (5). The recent approval of erdafitinib and the emergence of other potent and selective fibroblast growth factor receptor (FGFR) inhibitors has led to treatment improvement in advanced UC tumours harbouring FGFR3 or FGFR2 gene mutations (6).

Objective

In this review, we will focus on the rapid emergence of ICIs in the frontline and salvage therapy of advanced UC, particularly the anti-programmed cell death protein 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) inhibitors.

Rational for immunotherapy in advanced UC

UC of the bladder has long been known to be immune-responsive, with intravesical instillation of the Bacillus Calmette-Guerin (BCG) inducing cytotoxic T lymphocytes (CTLs) infiltration and promoting cell-mediated cytotoxicity against bladder tumour cells in subjects with non-muscle invasive bladder cancer. Despite decades of

research and clinical use, the mechanisms of BCG-induced immunotherapeutic effect have not been fully clarified due to the complexity of the multiple biological aspects involved, including the innate and adaptive immune systems (7). An effective anti-tumour immune response comprises a series of events: (I) release of tumour antigens from damaged or dying cancer cells; (II) uptake and presentation of these antigens by dendritic cells and other antigen-presenting cells; (III) priming and activation of T cells; (IV) trafficking, infiltration and enrichment of T lymphocytes and natural killer (NK) cells; (V) recognition and killing of cancer cell by CTLs and NK cells (8). This cycle provides a valid backbone for understanding the mechanisms of response and resistance to immunotherapy. For instance, therapeutic cancer vaccines and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibodies work by priming, activating, and expanding T cells, whereas ICIs such as anti-PD-1/PD-L1 monoclonal antibodies restore T-cell function against cancer cells, primarily blocking the interaction with the PD-L1 on the tumour cell, thus inhibiting immune escape and tumour growth (9). Apart from breast, ovarian and prostate cancer, DNA damage response alterations are also quite common in UC and have been extensively studied as potential predictive factors of response to cisplatin, but they are also likely to play a role in the response to immunotherapeutic agents (10-12). Tumour mutational burden (TMB) has been recognised as a predictive biomarker for response to immune therapy in various cancer types. UC exhibits a high degree of TMB in comparison with the majority of other solid malignancies, suggesting promising potential for the development of immunotherapeutic agents in UC (13). High PD-L1 protein expression in tumour cells and/or tumour infiltrating cells is associated with better treatment response to ICIs in a number of tumour types, including UC. Indeed, PD-L1 is the sole biomarker extensively adopted and validated in clinical practice to guide treatment decisions regarding the use of ICIs in the management of UC (14). The value of PD-L1 has been highlighted by the restriction of the indication of anti-PD-1/PD-L1 agents to UC first-line patients with high level of PD-L1 expression. Nevertheless, the predictive value of PD-L1 expression is quite limited, which may be partially due to the dynamic expression and heterogeneity within the tumour microenvironment (14-16). For instance, there seems to be high degree of discordance in PD-L1 expression between primary and metastatic UC lesions (16). The accuracy of PD-L1 as a predictive factor of response to ICIs has been studied in several cancer types adopting different PD-L1

diagnostic assays, antibodies, scoring algorithms, and cut-offs to measure PD-L1 expression in either tumour cells, immune cells or both, thus leading to some variability in results (15). Further studies are warranted to develop a reliable predictive model using PD-L1 expression and other biomarkers in UC. In addition to the benefit provided by ICIs and other immunotherapy agents in terms of efficacy outcomes, the increased quality of life in cancer patients receiving immunotherapy is usually higher than in those treated with standard cytotoxic chemotherapy, thus reinforcing the rationale for the clinical implementation of immunotherapy drugs in advanced UC (17).

Incorporation of ICIs into first-line and maintenance therapy in UC

ICIs are now a standard of care in first-line UC for cisplatin-ineligible patients. The phase II KEYNOTE-052 trial (18) investigated pembrolizumab as first-line therapy in 370 advanced UC patients who were ineligible for cisplatin-based chemotherapy. Encouraging findings from the updated analysis of this study showed an overall response rate (ORR) of around 28.6%, with around 5% of patients experiencing complete response (CR), and a median overall survival (OS) of 11.3 months (19). The safety data were comparable with the known safety profile of pembrolizumab, with around 15–20% Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 treatment-related adverse events (19,20). However, pembrolizumab was not found to improve OS in the phase III KEYNOTE-361 trial (2), which randomised around 1,000 first-line advanced UC patients to receive treatment with either pembrolizumab monotherapy, pembrolizumab plus platinum-based chemotherapy, or chemotherapy alone. After a median follow-up of 31.6 months, the median OS was quite similar among the three arms, reaching 15.6, 17.0, and 14.3 months, respectively. Similar data were published for atezolizumab in first-line advanced UC. The phase II IMvigor210 trial (21) evaluated atezolizumab in 119 advanced UC patients who were ineligible for cisplatin-based chemotherapy. The results from this study showed an ORR of 23%, with 9% of patients showing CR. Once again, the initial enthusiasm was hampered by the phase III trial data. In the IMvigor130 multicentre, phase III trial (20), untreated adult patients with advanced UC were randomly assigned to receive atezolizumab plus platinum-based chemotherapy (group A), atezolizumab monotherapy (group B), or placebo plus platinum-based chemotherapy (group

C). Preliminary median OS was 16.0 months in group A, 15.7 months in group B, and 13.1 months in group C. Updated interim analysis showed numerical but not statistical median OS advantage for atezolizumab monotherapy (22). In 2018, the Food and Drug Administration (FDA) issued a safety notice for the use of first-line pembrolizumab and atezolizumab, warning that decreased survival from the use of these agents in comparison with platinum-based chemotherapy was found in preliminary analysis of the two phase III trials (KEYNOTE-361 and IMvigor130). Therefore, the FDA prescribing information of atezolizumab and pembrolizumab was restricted to cisplatin ineligible patients with high PD-L1 expression or patients ineligible to any platinum-based therapy (either cisplatin or carboplatin), regardless of PD-L1 status (23). Specific PD-L1 expression scores have been developed and implemented to better identify patients eligible to such agents. Differences in antibodies used, implemented platforms and testing algorithms have raised questions about interchangeability and comparability among these assays and their diagnostic applicability. However, PD-L1 expression remains crucial in selecting first-line patients and remains the only factor widely adopted to predict clinical benefit from ICIs in advanced UC (14,15). According to European Medicine Agency (EMA) and the National Institute for Health and Care Excellence (NICE), pembrolizumab and atezolizumab are currently approved as monotherapies for the treatment of locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 or tumour-infiltrating immune cells score (IC) ≥ 5 , respectively (24,25). Several other trials have been investigating ICIs as first-line therapy for advanced UC given as monotherapy or combination, but so far there have been no trials showing clear superiority over cisplatin-based standard therapy. In the DANUBE phase III trial (26), durvalumab monotherapy or in combination with tremelimumab failed to show increased survival when compared with standard of care platinum-based chemotherapy in untreated advanced UC patients. Similarly, the combination of nivolumab and ipilimumab did not improve OS versus standard chemotherapy in the front-line setting for patients with advanced UC whose tumor cells express PD-L1 $\geq 1\%$, according to findings from the CheckMate-901 trial (27). In the KEYNOTE-361 trial mentioned above (2), pembrolizumab in combination with chemotherapy failed to show a survival benefit in comparison with standard chemotherapy. Despite the initial

activity often observed with platinum-based chemotherapy, most advanced UC patients will ultimately experience disease progression, with the majority of them being unable to receive second-line anti-cancer therapy due to clinical deterioration (28,29). Immunotherapy given as maintenance would increase the chance of advanced UC patients to receive clinical benefit from additional treatment while still retaining good performance status. In the phase III, multicentre, double-blind, controlled JAVELIN Bladder 100 clinical trial (30), 700 advanced or metastatic UC patients who did not have progressive disease following platinum-based first-line treatment, were randomly assigned to receive either maintenance avelumab or best supportive care. Avelumab was administered at a dose of 10 mg per kilogram of body weight intravenously every 2 weeks. Infusion-related reactions are reported in up to 30% of patients treated with avelumab, which is higher than the rate usually reported with other ICIs. Therefore, antihistamine and acetaminophen were administered approximately 30 to 60 minutes before at least the first four infusions. The primary objective of the study was to assess whether avelumab maintenance would increase OS in both the overall population and among patients with PD-L1 positive expressing tumours. Progression-free survival (PFS), ORR and other efficacy outcomes were selected as secondary endpoints. In the overall population, OS was significantly longer in patients treated with avelumab (median OS 21.4 *vs.* 14.3 months; $P=0.001$). The survival benefit was maintained among patients with PD-L1 negative tumours and all the other protocol-specified subgroups. PFS was also longer in the experimental arm, when compared with the control group (median PFS 3.7 *vs.* 2.0 months; $P<0.05$). The safety profile was manageable and comparable with the known characteristics of ICIs. Fatigue, pruritus, diarrhoea, hypothyroidism, skin rash and infusion-related reactions were the adverse events more frequently attributable to avelumab. Taken together, these data support the adoption of avelumab maintenance as a standard of care in advanced UC patients whose disease has not progressed on first-line platinum-based therapy. Overall, PD-L1 or PD-1 inhibitor monotherapy has been incorporated into the standard of care of first-line UC or maintenance, whereas these agents have so far not provided additional positive results when combined with either chemotherapy or CTLA-4 inhibitors (23,24). It is unclear whether different PD-1 or PD-L1 inhibitors are entirely comparable in terms of efficacy, as no trials comparing efficacy among these agents exist. Metanalyses and indirect comparisons from

clinical trials including patients with multiple tumour types may suggest some superiority in terms of PFS and OS for PD-1 inhibitors when compared to PD-L1 inhibitors (31). However, there are no valuable data supporting similar conclusion specifically to the UC population.

ICIs as second-line therapy in UC

UC patients progressing to first-line treatment have particularly poor prognosis and limited treatment options. Non-platinum chemotherapies given as monotherapies, such as taxanes or vinflunine, have been the standard of care before the approval of immunotherapy. Previous real-world data suggested that best supportive care was actually a very commonly adopted approach for second-line treatment in UC (28,29). ICIs have recently redefined the treatment landscape in this setting, as capable of providing patients with slightly longer median OS than chemotherapy and median duration of responses exceeding 12 months in UC patients experiencing partial response (PR) or CR (24). In the KEYNOTE-045 phase III trial (32), 542 advanced UC patients progressing after first-line platinum-based chemotherapy were assigned to receive either pembrolizumab or the physician's choice of second-line chemotherapy with paclitaxel, docetaxel or vinflunine. Pembrolizumab significantly prolonged median OS in the overall population (10.3 *vs.* 7.4 months; $P=0.002$). Furthermore, lower incidence of treatment-related adverse events was reported in the experimental group. Therefore, pembrolizumab is an approved treatment option in the second-line setting. Similar results were obtained by atezolizumab in UC post-platinum treatment. Following the encouraging results obtained in the phase II IMvigor210 trial cohort 2 (18), the results obtained in the randomised phase III IMvigor211 study (33,34), however, did not exhibit statistically significant longer median OS in comparison with standard second-line chemotherapy. Therefore, Genentech/Roche voluntarily withdrew the U.S. indication of second-line atezolizumab in advanced UC (35). Nivolumab, durvalumab and avelumab were also studied in phase I/II studies enrolling advanced UC patients progressing after first-line platinum-based chemotherapy and showed efficacy and safety comparable to the data obtained in different trials by atezolizumab and pembrolizumab, with median OS of around 8–10 months and ORR 10–25%. In these trials, PD-L1 expression level was not associated with significantly higher efficacy of ICIs, and therefore patient selection according to PD-L1

Table 1 Second-line immune checkpoint inhibitors for metastatic UC. Results from most representative trials

Trial name	Trial phase	Experimental arm	Efficacy outcomes
Keynote-045	3	Pembrolizumab 200 mg IV every 3 weeks (n=266)	ORR 21.9% mPFS 2.1 months mOS 10.3 months
IMvigor211	3	Atezolizumab 1,200 mg IV every 3 weeks (n=467)	ORR 23% mPFS 2.1 months mOS 11.1 months
Checkmate 275	2	Nivolumab 240 mg IV every 2 weeks (n=270)	ORR 20.7% mPFS 1.9 months mOS 8.6 months
Study 1108	1/2	Durvalumab 10 mg/Kg IV every 2 weeks (n=191)	ORR 17.8% mPFS 1.5 months
JAVELIN Solid Tumour	1/2	Avelumab 10 mg/kg IV every 2 weeks (n=44)	ORR 16.5% mPFS 1.5 months mOS 7.0 months
NCT04004221	2	Tislelizumab 200 mg IV every 3 weeks (n=113)	ORR 24% mPFS 2.1 months mOS 9.8 months

UC, urothelial carcinoma; IV, intravenous; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival.

status is not routinely advised when using these products in second-line treatment for advanced UC (23,36-39) (*Table 1*). More recently, the anti-PD-1 monoclonal antibody tislelizumab was engineered to minimize linking to the Fc gamma receptor on macrophages in order to mitigate antibody-dependent phagocytosis, a postulated mechanism of T-cell clearance and treatment resistance. Tislelizumab was studied in Asian UC patients previously treated with platinum-containing chemotherapy. The ORR observed was 24%, with median PFS and OS times of 2.1 and 9.8 months, respectively (40). These results led to the approval of tislelizumab by the China National Medical Products Administration (NMPA) as a second-line treatment for advanced UC patients, and this drug may also enter the European Union (EU) market in the near future.

Innovative approaches and drugs under clinical development

The development of novel, effective treatment options remains an important area of unmet need, especially for

patients who are cisplatin-ineligible. Apart from ICIs, enfortumab vedotin is one of the most promising drugs in the UC scenario. Enfortumab vedotin is an antibody drug conjugate directed against nectin-4, which is overexpressed in most UCs. Monomethyl auristatin E, an anti-microtubule agent, is the chemotherapeutic part linked to the monoclonal antibody. Enfortumab vedotin has shown to be quite active in advanced UC, showing remarkable anti-tumour activity in patients already exposed to platinum-based chemotherapy and ICIs (5). Preclinical data show that antibody drug conjugates may increase tumour immunogenicity by induction of immunogenic cell death, enhanced tumour antigen presentation, and tumour infiltration (41). Therefore, combining enfortumab vedotin with an ICI might improve the response rate and act synergistically in order to prolong PFS and OS in patients with advanced UC. The combination of enfortumab vedotin and pembrolizumab was tested in the EV-103 trial (42), showing a staggering response rate of 64.5% in the first-line setting. The EV-302 trial (43) is a two-arm, open-label, randomized controlled phase III study investigating

enfortumab vedotin in combination with pembrolizumab versus chemotherapy in previously untreated advanced UC. The trial results may pave the way for a new standard of care in the first-line setting. Sacituzumab govitecan is an emerging antibody drug conjugated targeting TROP-2, which is widely expressed in normal urothelium and most UCs. In the TROPHY-U-01 phase II trial, patients with advanced UC pre-treated with platinum-based chemo and ICI were included in cohort 1. Patients were treated with sacituzumab govitecan monotherapy and obtained sufficient anti-tumour activity (ORR of 27%) to be granted accelerated FDA approval (44). An encouraging 34% ORR was reported in cohort 3, enrolling patients progressed after platinum-based regimens and investigating sacituzumab govitecan in combination with pembrolizumab (45). ICIs in combination with tyrosine kinase inhibitors is an attractive field of investigation in several tumour types including UC, particularly in the setting of cisplatin-ineligible patients (46). In the phase III LEAP-011 trial (47), however, the combination lenvatinib plus pembrolizumab recently failed to show superior anti-tumour activity when compared with placebo plus pembrolizumab as frontline therapy in advanced UC patients who were ineligible to cisplatin. Additional combinations are still under investigation, including cabozantinib in combination with pembrolizumab or other ICIs (46). UC has been shown to express FGFRs. FGFRs are a family of receptor tyrosine kinases involved in tumour proliferation and cancer cell migration (48). FGFR3 is the most frequently hyperactivated of the FGFRs in UC, and its genetic alterations are found in around 20% of advanced UC. FGFR inhibitors target these receptors and show promise as a drug class. Erdafitinib, a pan-FGFR tyrosine kinase inhibitor, was shown to be clinically active and tolerable in patients with advanced UC and prespecified FGFR alterations in the BLC2001 study, leading to the regulatory approval of this drug (49). Literature evidence suggests that ICIs may have inferior response in UC harbouring FGFR alterations, possibly due to factors related to the tumour microenvironment (50-52). Several ongoing trials are still evaluating FGFR inhibitors in advanced UC, including the ongoing phase Ib/II NORSE trial combining erdafitinib plus the ICI cetrelimab in cisplatin-ineligible patients. Preliminary results presented at the European Society for Medical Oncology (ESMO) Congress 2022 showed promising anti-tumour activity for the combination (53). Cancer vaccines represent another way to activate the immune system, eliciting specific antibodies or cytotoxic immune responses directed against

cancer cells. UC has quite a long and rewarding history of vaccines use, starting from the BCG, which still represents a milestone for the treatment of non-muscle invasive bladder cancer since its introduction more than 30 years ago (7). In advanced UC, preliminary studies have mainly tested cancer vaccines in the forms of dendritic cells and peptide vaccines, but these products have so far been unsuccessful in progressing to later phases of drug development due to the modest clinical activity observed (54). The combination of cancer vaccines with other regimens would warrant further investigation, as it could potentially maximize the benefit of this type of therapy. For instance, NeoPepVac (55) is an ongoing pivotal trial investigating the safety and activity of a personalised neo-antigen vaccine containing up to 15 peptides obtained from the individual patient's tumour. In this study the cancer vaccine is being combined with an anti-PD-1 or anti-PD-L1 agent in advanced solid tumours, including patients with UC. Tumour-infiltrating lymphocyte (TIL) therapy is one of the several treatment modalities known collectively as adoptive cell therapy, which involves harnessing the patient's own immune system to obtain anti-tumour activity. TILs are collected from the tumour during a biopsy or surgical resection, and then stimulated and expanded to very large numbers *in vitro* with interleukin-2 (IL-2). The patient undergoes lymphodepletion with a brief course of chemotherapy before the infusion of the laboratory-grown TILs. TIL therapy has already shown to have remarkable anti-cancer activity in haematological malignancies, melanoma, and cervical, lung and head and neck cancers (56-60). It is hoped that further progress in TIL therapies will improve response rates further and enable this innovative treatment modality to become an available option across a wider range of solid malignancies, including UC (61,62). Historically, high-dose IL-2 therapy has been able to confer sustained clinical benefit in selected patients with immunogenic cancers such renal cell carcinoma and melanoma, partly through lymphoid expansion. Nevertheless, it is associated with severe toxicity requiring in-patient administration at specialist centres, thereby limiting its use (63). Bempegaldesleukin is a CD122-preferential IL-2 pathway agonist that has shown capacity to induce proliferation and activation of T cells and NK cells in the circulation and tumour microenvironment, including increased expression of PD-1 on cancer cells, in patients with advanced solid tumours (64). In the recent phase II PIVOT-02 trial, bempegaldesleukin in combination with nivolumab showed good tolerability and

promising anti-tumour activity as first-line treatment in patients with advanced UC (65), but subsequent disappointing efficacy results in the phase II PIVOT-10 study and other phase III trials in renal cell carcinoma and melanoma led to the discontinuation of the development program of bempegaldesleukin (66). Exploring the role of novel predictive factors of response to ICIs is another important research strategy in advanced UC. Dostarlimab received FDA approval for the treatment of advanced gynaecological malignancies with mismatch repair deficiency or microsatellite instability (67). Lynch syndrome, commonly known as hereditary non-polyposis colorectal cancer, is an autosomal-dominant familial cancer syndrome with an increased risk of UC. Indeed, there are limited reports suggesting that individuals with Lynch syndrome-related UC may receive significant benefit from ICIs (68). Baseline or early change in neutrophil-to-lymphocyte ratio has shown the potential to identify patients that may benefit the most from ICIs (29,69,70). Gut microbiome is emerging as a key factor in determining the balance between human health and disease (71). Growing literature evidence supports that microbiome heavily affects the therapeutic efficacy of cancer immunotherapy, particularly ICIs (72). Ongoing research is aiming at further exploring the field, and hopefully the manipulation of the gut microbiome may help enhancing the efficacy of immunotherapy in advanced UC and other malignancies in the future.

Conclusions

ICIs are revolutionising the systemic treatment of many malignant tumours, including advanced UC, providing durable responses with a favourable safety profile. Apart from PD-L1 expression, there remains an unmet need for successful implementation of valuable predictive factors that may optimise treatment selection. The immunomodulatory effect of the gut microbiome, for instance, is emerging as a critical factor and could potentially cover this unmet need. UC is undoubtedly chemosensitive, and platinum-based chemotherapy still retains a significant role in the management of advanced/metastatic disease. However, ICI combined with enfortumab vedotin and/or FGFR inhibitors may change the current scenario in the near future, whereas further research is warranted in order to implement novel immunotherapy modalities in the therapeutic armamentarium.

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