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Review

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The role of modern immunotherapy in metastatic urothelial cancer: mini review

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Abstract

The approval of immune checkpoint inhibitors (ICIs) has changed the treatment landscape in many aspects of urothelial cancer (UC), in both non-muscle-invasive bladder cancer and muscle-invasive bladder cancer and has introduced the concept of long-term remission for some patients in the metastatic setting. Front-line chemotherapy remains superior at achieving initial control of disease compared to front-line immune therapy. However, long-term durable responses are limited by chemotherapy resistance. The maintenance approach, sequencing chemotherapy with ICIs, could be considered a best of both worlds approach, achieving initial control with chemotherapy, which is maintained in some individuals with avelumab. However, outcomes for patients with metastatic UC remain poor. There are three steps to improving outcomes for these patients; the first is to develop better drugs and combinations of therapies, the second is the development of novel biomarkers and techniques to better select patients for treatment, and the third area of development is to give the drugs in the most optimal setting.

Keywords: Metastatic urothelial cancer, bladder cancer, immune therapy, immune checkpoint inhibitors, biomarkers

INTRODUCTION

The standard of care for first-line treatment of metastatic urothelial cancer (mUC) is platinum-based chemotherapy, namely cisplatin, for patients who meet eligibility cisplatin criteria[1]. The approval of immune checkpoint inhibitors (ICIs) has changed the treatment landscape in many aspects of urothelial cancer[2]. In the metastatic setting specifically, programmed death receptor-1 (anti-PD-1) and programmed death ligand-1 (anti-PD-L1) agents have been approved for patients who have progressed on front-line, platinum-based chemotherapy, and also for use in the front-line setting for patients who are ineligible to receive platinum-based chemotherapy, whose tumors express the PD-L1 biomarker[3]. Avelumab (an anti-PD-L1) has more recently been approved as maintenance therapy for patients who achieve response or stable disease following first-line chemotherapy. ICIs also have a role in non-metastatic UC[3-5]; however, the focus of this review article is on the role of ICIs in the metastatic setting, specifically.

OVERVIEW OF TREATMENT LANDSCAPE

Chemotherapy

Platinum-based chemotherapy combination remains the standard of care for treatment-naïve mUC patients[1,3]. The most used regimes are gemcitabine plus cisplatin, or alternatively, gemcitabine plus carboplatin, if patients are cisplatin-ineligible. Patients are eligible to receive cisplatin if they are in good physical condition, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, without significant comorbidities (> grade 2 hearing loss, > grade 2 neuropathy and/or New York Heart Association Class > III heart failure) and have adequate renal function, i.e., with creatinine clearance greater than 50-60 mL/min[6]. An alternative regime of accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination is also an acceptable option[6]. Six cycles of chemotherapy are considered standard of care, but fewer are acceptable in the case of cumulative toxicity[7]. Chemotherapy achieves good initial disease control (i.e., no disease progression on initial CT imaging) in the majority of patients (75%-80%), but long-term survival with chemotherapy agents alone remains poor due to chemotherapy resistance, with a median overall survival (OS) of 14-15 months and 9-10 months with cisplatin and carboplatin regimes, respectively[8-11].

Early trials in immune therapy

The use of ICIs, in particular, focusing on ICIs which target PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) has contributed to improved survival outcomes in patients with mUC[12]. PD-L1 positive mUC exhibits immune-escape mechanisms by binding to PD-1 on activated CD8+ T cells and exerting an immune-inhibitory effect. Therefore, monoclonal antibodies which block the interaction between PD-L1 (expressed on tumor cells and antigen-presenting cells (APCs) such as nivolumab, pembrolizumab and cetrelimab, and PD-1 (expressed on activated CD8+ T cells) such as atezolizumab, avelumab and durvalumab, remove this immunosuppressive effect within the tumor microenvironment and restore the antitumor cytotoxic T-cell immune response. Another immune checkpoint molecule that has been extensively studied in UC is CTLA-4, which is impressed on T cells exclusively. CTLA-4 inhibitors include ipilimumab and tremelimumab.

Similar outcomes have been reported from phase I-II studies for the use of ICIs in platinum-refractory disease and are outlined in Table 1. Response rates range from 15%-27% and show some PD-1/PD-L1 biomarker enrichment. Collectively, the agents show short progression-free survival (PFS) but promising OS signals with a good safety profile.

Pembrolizumab (anti-PD-1) displayed anticancer activity in the Phase 1b KEYNOTE-012 study (NCT01848834) with an overall response rate (ORR) of 27% and a median OS of 13 months

Table 1. Summary of second-line single-arm Phase I/II trials of immune checkpoint inhibitors in mUC

First author	Trial	Phase	Treatment line	Drug name	Sample size	Median follow-up (months)	Overall response rate (ORR)	Duration of response (months) (95%CI)	Median PFS (months) (95%CI)	1 year OS (%)	Median OS (months) (95%CI)
Plimack *et al.*, 2017[13]	KEYNOTE-012 NCT01848834	Ib	Second	Pembrolizumab	33	13.0	27.0%	10.0 (4.0-22.0)	2.0 (2.0-4.0)	50.0%	13.0 (5.0-20.0)
Petrylack *et al.*, 2018[14]	NCT01375842	I	Any	Atezolizumab	95	37.8	26.0%	22.1 (2.8-> 41.0)	2.7 (1.4-4.3)	45.0%	10.1 (7.1-17.0)
Rosenberg *et al.*, 2016[15]	IMvigor 210 NCT02108652	II	Second/cisplatin ineligible	Atezolizumab	310	11.7	15.0%	Not reached (2.0-13.7)	2.7months (2.1-3.9)	36.0%	7.9 (6.6-9.3)
Apolo *et al.*, 2017[16]	JAVELIN solid tumor NCT01772004	Ib	Second	Avelumab	44	16.5	18.2%	Not reached (12.1 - not estimable)	2.9 (1.5-4.4)	54.3%	13.7 (8.5-not estimable)
Patel *et al.*, 2018[17]	JAVELIN Solid tumor NCT01772004	Ib	Second	Avelumab	249	9.9	17.0%	Not reached (10.5 - not estimable)	1.6 (1.5-2.5)	NR 6 month OS 53.0%	6.5 (4.8-9.5)
Massard *et al.*, 2016[18]	NCT01693562	I/II	Second	Durvalumab	61	4.3	31.0%	Not reached (1.0-12.3)	Not reached	Not reached	Not reached
Powles *et al.*, 2017[19]	NCT01693562	I/II	First/second	Durvalumab	191	5.8	17.8%	Not reached (0.9-> 19.9)	1.5 (1.4-1.9)	55%	18.2(8.1 -not estimable)
Sharma *et al.*, 2016[20]	CheckMate032 NCT01928394	I/II	Second	Nivolumab	78	15.2	24.4%	9.4 (5.7-12.5)	2.8 (1.5-5.9)	45.6%	9.7 (7.3-16.2)
Sharma *et al.*, 2017[21]	CheckMate 275 NCT02387996	II		Nivolumab	270	7.0	19.6%	Not reached (7.4-not reached)	2.0 months	Not reached	8.7

(95%CI: 5-20)[13]. Results from this study showed efficacy in terms of anticancer activity and an acceptable safety profile.

Atezolizumab (anti-PD-L1) monotherapy for patients with mUC showed a long-term durable response in Phase I study (NCT01375842) with an ORR of 26% and a median OS of 10.1 months (95%CI: 7.3-17)[14]. Atezolizumab after the failure of platinum-based chemotherapy also demonstrated a significantly improved ORR of 15% compared to control in the Phase II study IMvigor 210 (NCT02108652)[15].

Early trials against both targets show promising results for long-term remission in mUC, which supported further single-arm trials.

Avelumab (anti-PD-L1) was approved for use in patients with advanced/mUC after platinum-based chemotherapy. Results from the phase Ib JAVELIN Solid Tumor study (NCT01772004) showed promising antitumor activity with a reported ORR of 18.2%, a median OS of 13.7 months and a tolerable safety profile[16,17].

Durvalumab (anti-PD-L1) was originally approved based on a phase I/II open-label study (NCT01693562), demonstrating favorable efficacy and an acceptable safety profile in advanced/mUC. ORRs are reported as 31% and 17.8% in each analysis. The median OS was 18.2 months. Durvalumab was granted approval for use in patients with mUC based on the results of this study[18,19].

Nivolumab (anti-PD-1) monotherapy in patients with mUC, previously treated with platinum-based chemotherapy, also showed clinical benefit in mUC and an acceptable safety profile in both the phase I/2 trial CheckMate 032 (NCT01928394) and the phase II trial CheckMate 275 (NCT02387996), with ORR of 24.4% and 19.6%, respectively and median OS of 9.7months and 8.7 months, respectively[20,21].

All these data stem from studies and do not reflect real-world data. Due to impressive results from early phase trials, a number of these ICIs initially received accelerated approval by the US Food and Drug Administration (FDA) for advanced/mUC. However, more recent data in both the first-line setting and platinum-refractory disease have shown more modest response rates, and indeed some of these accelerated approvals have been removed. Specifically, single-agent pembrolizumab is approved in platinum-ineligible patients (who cannot receive gemcitabine/cisplatin or gemcitabine/carboplatin), whilst atezolizumab is approved for cisplatin-ineligible patients with PDL1+ disease. The European Medicines Agency (EMA) has approved both drugs for cisplatin-ineligible, PDL1+ patients. It is unlikely that single-agent ICIs will get EMA or FDA approval in front-line UC.

Prior to the availability of ICIs, second-line treatment was limited to further chemotherapy with vinflunine[22] or taxanes[23] (docetaxel or paclitaxel), although this approach is not associated with a clear survival benefit.

Randomized trials have since been conducted. Pembrolizumab was associated with a significantly longer OS of approximately three months compared to chemotherapy in patients with previously treated mUC in the phase III KEYNOTE-045 trial (NCT02256436)[24]. Atezolizumab, however, was not associated with significantly longer OS than chemotherapy in patients with PD-L1 positive, platinum-refractory mUC in the phase III trial IMvigor 211 (NCT02302807)[25]. OS did not differ significantly between patients in the atezolizumab group and those in the chemotherapy group; and the median OS in the atezolizumab and chemotherapy groups was 11.1 *vs.* 10.6 months, respectively, with the HR of 0.87 ($P = 0.41$).

There was an attempt to move the ICIs into the front-line setting[26-28]. The rationale for this is that only a minority of patients receive second-line therapy; at this point, the tumor is progressing rapidly, and the overall benefit of second-line treatment is modest. As demonstrated in Table 1, results for ICIs in the second-line setting are not significantly different from the phase II results of cytotoxic chemotherapy.

There were three broad attempts: the first was single-agent immune therapy, particularly in the biomarker-positive patients, the second was a combination of immune therapy with chemotherapy, and the third was maintenance immune therapy, sequenced after chemotherapy.

Front-line immune therapy

When one looks in detail at the front-line randomized trials, we start with the phase III trial DANUBE (NCT02516241). Durvalumab or a combination of durvalumab/tremelimumab (CTLA-4 inhibitor) was compared to chemotherapy in patients with previously untreated advanced/mUC. In the PD-L1 positive population, the median OS was 14.4 months in the durvalumab monotherapy group *vs.* 12.1 months in the chemotherapy group; and the HR was 0.89 (95%CI: 0.71-1.11; $P = 0.30$). In the durvalumab plus

tremelimumab group, the median OS was 15.1 *vs.* 12.1 months in the chemotherapy group, and the HR was 0.85 (95%CI: 0.72-1.02; $P = 0.075$), showing ICI monotherapy and ICI combinations were not superior to chemotherapy in the front-line setting[26].

The challenge around front-line immune therapy in the PD-L1 positive patients is that it became apparent from the randomized phase III studies that ICIs did not have a high enough response rate, even in the biomarker-positive patients, and thus could not be superior to chemotherapy. Indeed, chemotherapy initially performed better because the response rates were higher and PFS was longer; therefore, these have not yet shown superiority compared to chemotherapy alone.

Front-line immune/chemotherapy combinations

In the phase III trial KEYNOTE-361 (NCT02853305), patients were randomized to receive (1) pembrolizumab alone; (2) pembrolizumab plus chemotherapy; and (3) chemotherapy alone. The addition of pembrolizumab to standard-of-care chemotherapy in the front-line setting for patients with advanced/mUC did not significantly improve outcomes, with a median OS of 17.0 months in the combination group compared to 14.3 months in the chemotherapy group, with a HR of 0.86 (95%CI: 0.72-1.02, $P = 0.0407$). Median OS was also similar between patients receiving pembrolizumab monotherapy, with a median OS of 15.6 *vs.* 14.3 months with chemotherapy and a HR of 0.92 (95%CI: 0.77-1.11)[27].

Atezolizumab has also been tested in the front-line setting. Phase III trial IMvigor130 (NCT02807636) demonstrated that the addition of atezolizumab to platinum-based chemotherapy as first-line treatment prolonged PFS in patients with metastatic urothelial carcinoma. Median PFS was 8.2 months in the atezolizumab plus chemotherapy group *vs.* 6.3 months in the placebo plus chemotherapy group (HR 0.82, $P = 0.007$)[28]. However, no OS signal was observed, so atezolizumab cannot be considered a standard of care.

The combination of chemotherapy and immune therapy in KEYOTE-361 and IMvigor 130 for pembrolizumab and atezolizumab, respectively, showed two regimes (chemotherapy and immune therapy given concurrently) did not appear additive, and therefore there was no clear benefit. The reason why this is the case remains uncertain, but it may be a bladder cancer-specific issue.

Maintenance immune therapy

The addition of avelumab as maintenance within 10 weeks of completion of first-line chemotherapy has also been shown to significantly improve OS among patients with mUC who had diseases that had not progressed with first-line chemotherapy in the phase III JAVELIN Bladder 100 trial (NCT02603432). The addition of avelumab to best supportive care is associated with an increase in median OS from 14.3 to 21.4 months with avelumab and a HR of 0.69 (95%CI: 0.56-0.86, $P = 0.001$)[29].

Results from these randomized trials show that ICI monotherapy is not yet superior to chemotherapy in the front-line setting[30]. The third approach, the maintenance approach, appeared most attractive because the JAVELIN Bladder 100 trial had a significant survival advantage. However, it is important to point out that not all patients are eligible to receive maintenance avelumab due to progress on chemotherapy. Therefore, subsequent approaches in the future include a combination of antibody-drug conjugates (ADCs) plus immune therapy[31], CTLA4 plus PD-L1 inhibition[32], and even the combination of FGFR plus immune checkpoint inhibition for the future (NORSE, NCT03473743).

Novel immune combinations

Novel Immune combinations are being explored. A potentially potent combination is pembrolizumab with sEphB4-HAS. Results from the phase II trial (NCT02717156) of pembrolizumab in combination with sEphB4-HSA in previously treated patients with mUC show an ORR of 37% in the overall cohort, with a complete response rate of 16%. In patients who are EprhinB2-positive, the results were attractive, with an ORR of 52% and CR of 24%. PFS and OS were also superior in the EphrinB2-positive patients at 5.7 and 21.5 months compared to 4.1 months and 14.6 months, respectively. The combination of pembrolizumab with sEphB4-HAS demonstrates synergistic activity and has also shown an acceptable toxicity profile. sEphB4-HAS exhibits antitumor action by inhibiting tumor growth factors EphB4 (expressed on tumor cells) and EphrinB2 (expressed on tumor vessels), thereby inhibiting tumor angiogenesis and survival. EphrinB2 is a new potential biomarker for identifying patients most likely to benefit from sEphB4-HSA-based therapy. The FDA has granted breakthrough approval for this combination since 2021. Randomized phase III trials are required[33].

Erdafitinib, a fibroblast growth factor (FGFR) tyrosine kinase inhibitor, has established clinical benefit in the second-line setting for patients with mUC and known FGFR mutations[34]. The combination of erdafitinib with anti-PD-1 cetrelimab in the NORSE study (NCT03473743) showed clinically meaningful responses in the first-line setting for cisplatin-ineligible, FGFR positive patients with mUC of 68% *vs*. 33 % (n = 37). NCT03473743.

Durvalumab has also been investigated in combination with various targeted therapy inhibitors (FGFR1,2,3, PARP, TORC 1 + 2) in the BISCAY study (NCT02546661). Biomarker analyses showed a correlation between circulating plasma-based DNA (ctDNA) and tissue biomarkers for FGFR DNA alterations. FGFR inhibition showed efficacy, but the addition of durvalumab did not appear to enhance this, questioning the immune/targeted therapy approach in mUC[35].

Combinations of ADCs plus immune therapy are also being explored. Enfortumab Vedotin (EV) binds to nectin-4, an extracellular adhesion protein significantly expressed on the surface of UC cells. EV as monotherapy in patients with mUC who had received previous platinum chemotherapy and immune therapy showed an OS advantage compared to chemotherapy [HR 0.70 (95%CI: 0.56-0.89; P = 0.001)] in the EV-301 study (NCT03474107)[36]. The combination ADCs together with immune therapy also shows promising new targets in phase I studies. The EV-103 study (NCT03288545) of EV in combination with pembrolizumab as first-line therapy for patients with mUC, ineligible to receive cisplatin, showed an ORR of 73.3%[29]. Results from the ongoing randomized study EV-302 (NCT04223856), comparing EV plus pembrolizumab to standard-of-care chemotherapy in the front-line setting, are awaited. Sacituzumab govitecan (SG), another ADC, has also been given as a single agent (TROPiCS-04, NCT04527991) and in combination with pembrolizumab (TROPHY U-01, NCT03547973)[37] Single agent and combination results in pre-treated patients showed response rates of approximal 27% and 35% respectively[37]. Further development of this agent is ongoing.

Circulating tumor DNA

An increasingly effective way to identify minimal residual disease is via circulating tumor DNA (ctDNA). It can be identified using different methods, both a panel-based approach where pre-defined genes are explored from plasma, or a personalized approach, whereby mutations are identified from the primary tumor and tracked from subsequent plasma analysis. The most recent data in urothelial cancer has used a personalized approach (Signatera), where up to 16 mutations are tracked. This was explored in the adjuvant setting for patients who received either placebo or atezolizumab (PD-L1 inhibitor). Results from the IMvigor010 study (NCT02450331) show that 40% of patients with no evidence of disease after cystectomy

were radiologically ctDNA-positive, and had a 6-fold increased risk of relapse. There was also a significant increase in death associated with ctDNA-positive[38]. One of the intriguing findings regarding this data is that it also showed a significant reduction in the risk of death in the ctDNA-positive patients who received atezolizumab compared to BSC, with a HR of 0.58 (95%CI: 0.43-0.79, P = 0.0024)[39]. Biomarker work revealed a link between the ctDNA and biomarkers such as PD-L1 in the primary tumor. These data are being validated in the ongoing IMvigor011 trial (NCT04660344).

Immune biomarkers

Immune therapy biomarkers were initially explored with PD-L1, with a plethora of different methods and antibodies. Results with PD-L1 expression in prospective randomized trials have been inconsistent and sometimes contradictory. The PD-L1 biomarker in isolation does not appear to be helpful across the board. While enrichment may occur in some studies, this tends to occur when the trial is positive, irrespective of the biomarker[5,29]. Other biomarkers remain exploratory and have not been the primary endpoint in prospective studies, the most promising of which is TMB and T-effector signatures. Other biomarkers such as APOBEC[40], TGFß, NK and macrophages have all also been explored[29,41]. Both innate and adaptive immunity appear relevant in determining response, and other indirect factors, such as angiogenesis signaling, may also be involved. It is likely that we have oversimplified biomarker analysis with PD-L1. Other avenues, including multi-platform techniques and tertiary lymphoid structures (TLS), may be relevant.

FUTURE

Immune therapy has changed the treatment landscape by introducing the concept of long-term remission for patients. However, as it currently stands, we lack the biomarkers to identify these patients, and we are introducing immune therapy late in the treatment pathway. Alternatives are required, including three steps. The first is to develop better drugs and better combinations of therapies. We are doing this with ADCs, immune therapy combinations and potentially FGFR combinations with immune therapy. Specifically, the NORSE trial looked at cetrelimab plus erdafitinib, with response rates of 68% in FGFR-positive patients. These data deserve further evaluation in a randomized phase III trial and suggest that the combination of ICI plus FGFR therapy may be additive in the front-line setting. Enfortumab vedotin shows exceptional response rates in the region of 70% in two trials. EV plus pembrolizumab is being tested in the EV302 study. This is predicted to be a positive trial and has a high chance of changing practice if it can reproduce the response rates of 70% in the phase II trial. There is still hope that CTLA4 will have a role in the future, which is being tested in the CheckMate901 trial (NCT03036098) and the NILE trial (NCT03682068) in biomarker-selected patients and in combination with chemotherapy. All these trials will provide extensive data on CTLA4 in urothelial cancer. There is a plethora of new ADCs, such as RC48[42] and sacituzumab govitecan, both of which have significant single-agent activity. Both agents are being combined with immune therapy and front-line randomized trials with these drugs, with a similar ethos to the EV302 trial, which is attractive.

The second area of focus is the development of better biomarkers. We are now beginning to understand the need for multi-platform techniques, and circulating, as well as tissue-based biomarkers. Single-cell RNA sequencing, spatial transcriptomics and multiomic analysis are all exciting biomarker platforms for the future, as well as circulating methylation signatures.

The third area of development in the future is giving the drugs in the right setting. It is apparent that second- and third-line platinum-refractory urothelial cancer patients are not the optimal choice to benefit from these drugs. Indeed, earlier in the disease process, potentially in the perioperative space, may be the

optimal setting where we can cure most patients. Specifically, by giving these patients multiple therapies pre-operatively, downstaging the disease and using monitoring biomarkers such as ctDNA and other types of adjuvant therapy, it is possible to cure more patients in the future.

ICIs also have a role in the management of both non-muscle-invasive bladder cancer (NMIBC)[4] and muscle-invasive bladder cancer (MIBC). Pembrolizumab (anti-PD-1) can be used in patients with BCG-unresponsive NMIBC who are not fit to undergo radical cystectomy (RC)[3]. Adjuvant nivolumab (anti-PD-1) has shown promising results following RC in patients with MIBC, but OS results are awaited before this treatment is recommended[5].

CONCLUSION

Front-line chemotherapy remains a more attractive option due to its superiority in initially achieving initial control of disease compared to first-line immune therapy. However, long-term durable responses are limited by chemotherapy resistance. The maintenance approach, sequencing chemotherapy with ICIs, could be considered a best of both worlds approach, achieving initial control with chemotherapy, which is maintained in some individuals with avelumab. Studies are ongoing to investigate whether earlier immune therapy improves outcomes for patients (DISCUS, EudraCT 2021-001975-17).

DECLARATIONS

Authors' contributions

Were responsible for content inclusion: Jackson-Spence F, Powles T
Did the academic write up: Jackson-Spence F
Were responsible for peer review and editing prior to submission: Toms C, Yang YH, Jurascheck L, Choy J, Flanders L, Szabados B
Had oversight of the project: Powles T

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All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

There is no direct patient involvement in this product therefore additional ethical submissions are not required.

Consent for publication

Not applicable.

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