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Review

Changes in the treatment landscape for metastatic urothelial cancer: current therapy and future directions

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Abstract

Despite the development of several new drugs, cisplatin-containing chemotherapy remains the standard frontline option for advanced urothelial carcinoma (UC). Since the cisplatin-based regimen became the standard therapy for metastatic UC, there have been few advances in chemotherapy, until recently. A better understanding of molecular pathobiology of UC and advances in cancer immunology have led to a sharp increase in clinical trials for metastatic UC with the rapidly changing systemic treatment for this disease. This review summarizes current chemotherapy and immunotherapy for metastatic UC, as well as novel agents and ongoing trials.

Keywords: urothelial carcinoma; cytotoxic chemotherapy; immunotherapy; targeted agent; antibody-drug conjugate; biomarker

1. Introduction

Urothelial carcinoma (UC) is a malignant tumor that develops in the urinary tract. Bladder cancer is the most common urinary tract cancer, followed by ureteral and urethral cancer [1]. In 2019, there were estimated to be approximately 80,000 new cases of bladder cancer in the USA, with approximately 18,000 deaths [2]. Bladder cancer is the sixth most common cancer in the USA; it is usually diagnosed in older patients (mean age of 70 years) [3]. Approximately 5% of UC patients have metastasis at the time of the initial diagnosis [3]. Platinum-based chemotherapy, usually in combination with gemcitabine, has been the standard frontline therapy for metastatic UC patients over the past 30 years [4–6]. However, the prognosis of metastatic UC patients is poor, with a median overall survival of approximately 15 months [7,8]. Furthermore, approximately half of bladder cancer patients are unfit for traditional cytotoxic chemotherapy because of poor general condition, cardiac and renal dysfunction, or neuropathy [9]. Recent advances in the understanding of cancer biology and tumor immunology have provided novel insights into the treatment of metastatic UC. Accumulated evidence regarding immune checkpoint inhibitors (ICIs) has led to the development of new drugs to treat various malignant tumors [10]. UC is a rapidly developing area of oncology, with recognition of biomolecular changes and the application of new drugs. Here, we conducted a brief review of current chemotherapy and new drugs along with biomarkers to predict the treatment response in patients with metastatic UC.

2. Cytotoxic chemotherapy for metastatic urothelial carcinoma

2.1 First-line cisplatin-based combination chemotherapy

Traditional cytotoxic chemotherapy is the main option for treatment of metastatic UC [11]. Among several chemotherapeutics, cisplatin is the main treatment agent based on an overall response rate of approximately 33% in patients with advanced or metastatic UC [12]. A response rate of 72% with a complete response (CR) rate of 36% was reported [13] in a phase II study of the combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC). In pivotal randomized phase III trials, MVAC was superior to cisplatin alone or in combination with cyclophosphamide and adriamycin; it has become the standard of care for metastatic UC [14,15]. However, MVAC is very toxic, with a mortality rate of 4% [13,14]. Therefore, a less toxic treatment with similar or better efficacy, compared to MVAC, is needed for metastatic UC. Many clinical trials have been conducted in this context. An objective response rate (ORR) of 47%, a CR rate of 18%, and median survival of 12.5 to 14.3 months were reported in patients with metastatic UC in a phase II trial of gemcitabine combined with cisplatin (GC) [16]. A randomized phase III study comparing GC and MVAC demonstrated comparable efficacy with regard to response (GC, 49.4% *vs.* MVAC, 45.7%), time-to-progression (GC, 7.4 months *vs.* MVAC, 7.4 months), and overall survival (OS) (GC, 13.8 months *vs.* MVAC, 14.8 months), but showed a favorable toxicity profile in patients treated with GC (Table 1, Ref. [6,17–22]) [6]. Therefore, GC is considered the standard treatment option for advanced or metastatic UC. In addition, several studies have evaluated the long-term outcomes of metastatic UC patients receiving either GC or MVAC. OS was comparable in both treatment groups with a median sur-

Table 1. Pivotal clinical trials in patient with metastatic urothelial carcinoma.

Agents	Type	Setting	Year	Phase (trial)	ORR/mPFS/mOS
Gemcitabin + cisplatin	Cytotoxic	First-line; cisplatin-fit	2000	Phase III [6]	49.4%/7.4 months/13.8 months
Dose-dense MVAC	Cytotoxic	First-line; cisplatin-fit	2006	Phase III [17]	64%/9.5 months/15.1 months
Gemcitabine + carboplatin	Cytotoxic	First-line; cisplatin-unfit	2012	Phase II/III [18]	42%/5.8 months/9.3 months
Pembrolizumab	Anti-PD-1	Second-line ICI; platinum-pretreated	2017	Phase III [19] (KEYNOTE-045)	21.1%/2.1 months/10.3 months
Avelumab	Anti-PD-L1	Maintenance ICI; after first-line chemotherapy	2020	Phase III [20] (JAVELIN Bladder 100)	-/3.7months/21.4 months
Ramucirumab + docetaxel	Anti-angiogenic + cytotoxic	Platinum-refractory	2017	Phase III [21] (RANGE)	22.2%/4.07 months/-
Enfortumab vedotin	ADC	Progressed on chemotherapy and ICI	2021	Phase III [22] (EV-301)	40.6%/5.55 months/12.88 months

MVAC, methotrexate, vinblastine, adriamycin, cisplatin; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; ADC, antibody–drug conjugate; ICI, immune checkpoint inhibitor; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival.

vival of 14.0 months for GC and 15.2 months for MVAC [7]. Fewer toxic deaths were observed among the population treated with GC than among the population treated with MVAC, although the difference was not statistically significant. Updated 5-year data showed no significant difference between GC and MVAC groups in terms of survival [7]. Based on these findings, cisplatin-based chemotherapy has become the standard frontline option for treatment of metastatic UC [7,14,15,23]. Another randomized phase III trial was conducted to compare dose-dense MVAC (ddMVAC) to standard MVAC (Table 1, Ref. [6,17–22]) [17]; the study demonstrated that 24.6% of patients were alive in the ddMVAC arm, compared to 13.2% in the standard MVAC arm, at a median follow-up of 7.3 years. These data suggest that ddMVAC had significantly better efficacy and a significantly better safety profile than did the original MVAC; therefore, the original MVAC is no longer recommended [17]. Overall, GC and ddMVAC are commonly used in first-line settings for advanced UC [4,7,23].

Reinforcement of the standard treatment was evaluated in clinical studies using paclitaxel combined with GC (PGC). A randomized phase III trial was performed to compare PGC to GC in patients with advanced UC; it demonstrated that PGC resulted in an improved tumor response and a survival benefit of 3.1 months, but these effects did not reach statistical significance [8].

2.2 First-line chemotherapy in cisplatin-unfit patients

More than half of bladder cancer patients are ineligible for cisplatin-containing chemotherapy because of poor general condition, cardiac and renal dysfunction, or neuropathy [24]. Patients with at least one of the following criteria are unsuitable for cisplatin-containing regimens: Eastern Cooperative Oncology Group performance status $\geq$2, creatinine clearance $<$60 mL/min, grade $\geq$2 hearing loss, grade $\geq$2 neuropathy, and/or New York Heart Association Class III heart failure [9]. Treatments with favorable safety profiles are recommended for cisplatin-unfit patients with UC. Carboplatin-based chemotherapies are usually accepted as alternatives to cisplatin-based chemotherapy in such patients [25–27]. Carboplatin is a platinum analog that is less nephrotoxic than cisplatin, but it appears to have a slightly weaker antitumor effect [28]. As an alternative, carboplatin can replace cisplatin in patients with decreased renal function. A randomized phase II/III trial was conducted to compare gemcitabine plus carboplatin (GCb) to methotrexate, carboplatin, and vinblastine (M-CAVI) in cisplatin-unfit advanced UC patients; the study showed ORRs of 42% for GCb and 30% for M-CAVI (Table 1, Ref. [6,17–22]) [18]. However, the median OS was 9.3 months in the GCb cohort *vs.* 8.1 months in the M-CAVI cohort (p = 0.64). No difference in progression-free survival (PFS) was observed (p = 0.78) between the two cohorts. The incidence of serious toxicity was higher for patients treated with M-CAVI [18]. Based on these data, GCb has become the standard treatment for cisplatin-ineligible patients with metastatic UC.

2.3 Salvage chemotherapy after first-line treatment failure

Metastatic UC is a chemosensitive tumor; cisplatin-based systemic treatment is the standard of care with clinical benefits. However, there are no established treatment options in a second-line setting; thus, frontline chemotherapy failure leads to an OS of 6–7 months [29]. Many agents have been tested as second-line treatments [30–39]. However, no successful phase III clinical trials have shown survival improvement of any palliative regimen over any other treatment or best supportive care (BSC). Vinflunine is the only successful cytotoxic drug that has been studied for mUC in a randomized phase III trial [29,40]. In the intention-to-treat population, the median OS was 6.9 months for vinflunine plus BSC *vs.* 4.6 months for BSC alone. In a multivariate analysis, vinflunine treatment was

associated with better survival (hazard ratio (HR)), 0.719; 95% confidence interval (CI), 0.570–0.906; p = 0.0052) [40]. Several chemotherapeutics, such as gemcitabine, docetaxel, and paclitaxel, have also been recommended [41–43].

3. Immunotherapy for metastatic urothelial carcinoma

The median OS in patients with metastatic UC taking a frontline cisplatin-based combination therapy is approximately 14 months [7]. However, the prognosis is dismal for patients with metastatic UC who progress after first-line therapy [29]. Therefore, alternative approaches for metastatic UC treatment are essential. Accumulated data from many studies suggest that immune checkpoint inhibition is useful for cancers with high somatic mutation rates, which may trigger several tumor-specific neoantigens [44,45]. DNA mutations in malignant tumor cells are reflected in the production of modified proteins, which enhance priming and activation of the host immune system [46]. The programmed cell death protein-1 (PD-1) signal is a negative feedback system that suppresses Th1 cytotoxic immune responses, which can damage the host if dysregulated [47–49]. Programmed cell death-ligand 1 (PD-L1) is upregulated in various cancers and the tumor microenvironment [50–52]. Inhibition of this pathway with anti-PD-1 or anti-PD-L1 antibodies has resulted in good tumor regression in patients with many types of cancer [44,53–58]. Data generated through The Cancer Genome Atlas (TCGA) show that bladder cancer has the third-highest mutation rate among all malignant tumors; therefore, ICIs have a critical impact as a treatment weapon for metastatic UC [59]. The FDA has approved PD-L1 and PD-1 inhibitors for the treatment of patients with UC [60].

3.1 First-line immune checkpoint inhibitors in cisplatin-ineligible patients

A multicenter, phase II study (KEYNOTE-052) assessed pembrolizumab as a first-line treatment in cisplatin-unfit patients with UC [61]. The ORR was 24% with a CR rate of 5%. Severe treatment-related adverse events (AEs) occurred in 16% of patients. First-line pembrolizumab showed antitumor activity and a favorable toxicity profile in cisplatin-unfit UC patients [61]. Atezolizumab was studied as a frontline treatment in 119 cisplatin-unfit patients with locally advanced or metastatic UC [62]. The ORR was 23% with a CR rate of 9%; the median OS was 15.9 months. Severe treatment-related adverse reactions occurred in 16% of patients [62]. However, the FDA issued a safety warning in May 2018 concerning the use of pembrolizumab and atezolizumab as first-line therapy. An initial review of the data generated by two clinical trials (KEYNOTE-361 and IMvigor130) demonstrated that patients treated with pembrolizumab or atezolizumab in a first-line setting have worse survival rates than do patients treated with a platinum-containing regimen [60]. Atezolizumab and pembrolizumab have been approved as a restricted first-line treatment option for patients with locally advanced or metastatic UC who are unfit for cisplatin-containing chemotherapy and whose tumors express PD-L1, or in patients who are unfit for any platinum-based systemic therapy regardless of PD-L1 status [63].

3.2 Second-line immune checkpoint inhibitors in platinum-pretreated patients

ICIs have demonstrated antitumor effects in patients with UC, with a favorable toxicity profile and durable response in a second-line treatment setting. A randomized, phase III trial was conducted to compare pembrolizumab to the investigator's drug choice (paclitaxel, docetaxel, or vinflunine) in 542 patients with platinum-refractory advanced UC [19]. This study demonstrated an improved OS for patients treated with pembrolizumab compared to chemotherapy (median, 10.3 months *vs.* 7.4 months, respectively; p = 0.002), with fewer grade 3 or 4 treatment-related AEs (Table 1, Ref. [6,17–22]) [19]. Long-term outcomes from this study were consistent with earlier reports, with better 1- and 2-year OS and PFS for pembrolizumab compared to the cytotoxic regimen [64].

Atezolizumab has also been investigated in metastatic UC patients after platinum treatment. A phase II trial (IMvigor210) evaluated the efficacy of atezolizumab in advanced UC patients [55]. The outcomes were analyzed based on PD-L1 expression of tumor-infiltrating immune cells (IC) using immunohistochemical staining. PD-L1 expression status was defined as the percentage of PD-L1-positive immune cells, as follows: IC0 (<1%), IC1 (1% to <5%), and IC2/3 (≥5%) [55]. In patients with platinum-failed metastatic UC, the IC2/3 population had a better ORR than did the other groups [10]. In 2016, atezolizumab was approved by the FDA for these patients. A recent randomized phase III trial (IMvigor211) compared atezolizumab to the investigator's drug choice (vinflunine, paclitaxel, or docetaxel) in platinum-failed advanced UC patients [65]. However, unlike previous studies, the OS of patients in the IC2/3 cohort did not differ between the atezolizumab and chemotherapy arms (11.1 months *vs.* 10.6 months, respectively; p = 0.41). Similarly, the ORRs were comparable between arms in this population. Although atezolizumab did not result in improved OS compared to chemotherapy, a more favorable toxicity profile was reported; 20% of patients experienced grade 3–4 treatment-related AEs, compared to 43% of patients receiving chemotherapy [65]. The phase IIIb SAUL study and another extended approach study investigated the safety and efficacy of atezolizumab in patients similar to the real-world population, including patients not suitable for the IMvigor211 trial [66,67]. The SAUL study confirmed the tolerability of atezolizumab in a real-world pretreated population with urinary tract cancer. The overall efficacy in the IMvigor211-like patient

group was similar to efficacies in previous key ICI studies, supporting the use of atezolizumab in urinary tract cancer [66,67]. In March 2021, the manufacturers of atezolizumab voluntarily withdrew their indication for platinum-treated advanced or metastatic UC, which was based on the failure of the IMvigor211 trial to improve OS as its primary outcome [65].

CheckMate 275 was a phase II trial to assess the efficacy and safety of nivolumab in patients with platinum-resistant advanced UC [68]. In this study, the ORR was 19.6% regardless of tumor PD-L1 expression, with a median OS of 8.74 months (95% CI, 6.05 to not reached). Grade 3 or 4 treatment-related AEs were reported in 18% of patients [68]. CheckMate 032 was an open-label multicohort trial that included patients with metastatic UC who received nivolumab [69]. In that study, the ORR was 25.6%; grade 3 or 4 treatment-related AEs occurred in 26.9% of patients who received nivolumab monotherapy [69]. Therefore, the FDA approved nivolumab in 2017.

Avelumab is a human monoclonal antibody targeting PD-L1, with antitumor efficacy in various cancers. A phase Ib study evaluated the safety and antitumor activity of avelumab in patients with platinum-resistant UC who were unselected because of PD-L1 expression. In that study, the confirmed ORR was 18.2% with five CRs and three partial responses [70]. The median PFS was 11.6 weeks, and the median OS was 13.7 months. Grade 3 or 4 treatment-related AEs occurred in 6.8% of the patients [70]. In the phase I JAVELIN Solid Tumor study, 249 patients with platinum-resistant metastatic UC or who were unfit for a cisplatin-containing regimen were enrolled. The ORR was 17% with a CR rate of 6% in 161 patients who had previously been treated with a platinum agent. Only 8% of the patients experienced grade 3 or higher treatment-related AEs [71]. Based on these data, the FDA granted accelerated approval of avelumab in 2017.

A phase I/II trial evaluated the safety and efficacy of durvalumab (anti-PD-L1 antibody) in platinum-resistant metastatic UC patients [72,73]. In that study, PD-L1-positive was defined as $\geq$25% of tumor cells or tumor-infiltrating ICs expressing membrane PD-L1. The ORRs were 31.0% in 42 response-evaluable patients, 46.4% in the PD-L1-positive subgroup, and 0% in the PD-L1-negative subgroup with manageable toxicities [72,73]. The FDA approved durvalumab in 2017.

3.3 Maintenance with immune checkpoint inhibitors after first-line chemotherapy

Many clinical trials have investigated the efficacies of ICIs in patients with platinum-resistant advanced UC, resulting in clinical benefits. However, in a phase III randomized trial (JAVELIN Bladder 100), maintenance ICI was investigated in patients with advanced UC [74]. That study demonstrated superior OS with avelumab maintenance *vs.* BSC alone in patients with UC who had disease that had not progressed with frontline chemotherapy (median OS, 21.4 *vs.* 14.3 months, respectively; $p = 0.001$). Both PFS and ORR improved significantly in the avelumab group (Table 1, Ref. [6,17–22]) [20,75]. Improvement in OS parameters led to FDA approval of avelumab as maintenance therapy for metastatic UC in 2020.

4. Targeted therapies for metastatic urothelial carcinoma

4.1 Anti-angiogenics

Similar to tissue repair and wound healing, tumorigenesis requires the development of a neovascular system and suppression of excessive inflammation [76]. The concept of synergistic angiogenesis and immunosuppression can be applied to develop novel cancer treatments by exploiting the tumor microenvironment [77]. This paradigm is increasingly associated with state-of-the-art immunotherapy strategies for cancer [78]. A three-arm randomized controlled trial was conducted to compare the efficacy of docetaxel monotherapy to docetaxel plus ramucirumab (human IgG1 VEGFR-2 antagonist) or icrucumab (human IgG1 VEGFR-1 antagonist) in platinum-resistant advanced UC patients [79]. Docetaxel and ramucirumab combination therapy significantly improved PFS [79]. The phase III RANGE trial investigated the efficacy and safety of treatment with docetaxel plus either ramucirumab or placebo in patients with platinum-refractory advanced UC [21]. The primary analysis in that study showed a significant improvement in PFS after the addition of ramucirumab (median OS, 4.07 *vs.* 2.76 months, respectively; $p = 0.0118$) (Table 1, Ref. [6,17–22]) [21].

Cabozantinib inhibits specific receptor tyrosine kinases; it suppresses metastasis, angiogenesis, and oncogenesis [80]. A phase I trial was performed to evaluate the safety and efficacy of cabozantinib plus nivolumab (CaboNivo) compared to CaboNivo plus ipilimumab in patients with advanced UC and other genitourinary cancers [81]. In patients with metastatic UC, the ORR (38.5%) was superior to single-agent ICI (15%–20%) or cabozantinib (19%), with a disease control rate of 92.3%, median PFS of 12.8 months, and median OS of 25.4 months [81]. Several studies are ongoing for these combined treatments.

4.2 Fibroblast growth factor receptor inhibitors

Previous studies identified many genomic changes in UC, and TCGA data demonstrate that UC has the third-highest mutation rate among malignant tumors [82]. A genomic profile-based assessment of advanced UC showed that 93% of patients had at least one clinically relevant genomic change, with a mean of 2.6 clinically relevant genetic changes [83]. The most common clinically relevant modifications involved cyclin-dependent kinase inhibitor 2A (*CDKN2A*) (34%), fibroblast growth factor receptor 3 (*FGFR3*) (21%), phosphatidylinositol 3-kinase catalytic subunit alpha (*PIK3CA*) (20%), and *ERBB2* (17%) [83]. Of

the *FGFR3* changes, 53 (84%) were *FGFR3* base substitutions, two (4%) were truncation mutations, one (1%) was a gene amplification, and seven (13%) were gene rearrangements and fusions. Amplifications, mutations, and gene fusions of the FGFR genes *FGFR1* and *FGFR3* have been identified in 77 UC cases (26%), representing the most frequent modification of a signaling pathway [83]. FGF signaling enhances cancer development by modulating a range of major downstream biological cascades. FGFR1 is an upstream controller of the Akt, MAPK, and RAS pathways; it is involved in regulating the cell cycle and angiogenesis [84].

Erdafitinib is a small molecule inhibitor of FGFR. A phase II BLC2001 study of the ORR in patients with pretreated metastatic or unresectable *FGFR* altered-positive UC [85] revealed an ORR of 40% and a CR rate of 3%. Notably, the ORR was 59% among the 22 patients treated with a previous ICI. The median PFS was 5.5 months, and the median OS was 13.8 months. Erdafitinib was well tolerated and no treatment-related deaths occurred [85]. Based on this study, erdafitinib was granted a breakthrough therapy designation by the FDA for the treatment of advanced UC in 2019. A randomized phase III BLC3001 study compared erdafitinib to vinflunine, docetaxel, or pembrolizumab for patients with advanced UC who had selected *FGFR* gene alterations.

The activation of FGFR signaling is associated with non-T cell-inflamed tumors in muscle-invasive bladder cancer [86]. The non-T cell-inflamed tumor microenvironment is related to a poor prognosis and treatment resistance to immunologic agents [87]. Thus, ICIs may be less active in FGFR-activated UC. Several experimental studies have shown that erdafitinib inhibits FGFR signaling, enhances T cell infiltration, suppresses regulatory T cells, and decreases PD-L1 expression in cancer cells [88]. Thus, combining erdafitinib and ICI induces the expansion of T cell clones and immunological response in the tumor microenvironment to enhance antitumor activity [88]. Several clinical trials are ongoing in this context. In a phase Ib/II trial assessing the combination of vofatamab, a selective FGFR3 inhibitor, with pembrolizumab in metastatic UC, vofatamab combined with pembrolizumab was well tolerated with promising tumor response and improved PFS in the wild-type cohort [89]. Rogaratinib is a small molecule inhibitor of FGFR1-4. In a phase I study, rogaratinib showed encouraging efficacy and safety in advanced UC patients with *FGFR1-3* mRNA overexpression [90]. FORT-2 is a phase Ib/II study that aims to evaluate the safety and efficacy of rogaratinib in combination with atezolizumab in cisplatin-unfit, *FGFR*-positive, advanced/metastatic UC [91].

5. Antibody-drug conjugates

The treatment options are limited for UC patients who have progressed on chemotherapy and ICIs [4]. Thus, novel effective therapies are needed for these patients. Enfortumab vedotin (EV) is the first-in-class antibody-drug conjugate directed against nectin-4, a protein located on the surface of cells that is highly expressed in bladder cancer [92,93]. EV binds to nectin-4-expressing cells, followed by the internalization and release of the antimitotic agent monomethyl auristatin E (MMAE) into the cell via lysosomal cleavage. MMAE disrupts the microtubular system, thereby preventing the cell cycle and inducing programmed cell death [92].

EV-201 was a pivotal phase II study of EV in patients with locally advanced or metastatic UC who progressed on or after platinum and/or ICI therapies [94]. The confirmed ORR was 44%, with a 12% CR rate. The ORRs were 41% in ICI non-responders and 38% in patients with liver metastasis. EV was well tolerated with a manageable toxicity profile [94]. EV-301 was a phase III trial of EV *vs.* the investigator's choice of chemotherapy in patients with advanced UC who had progressed on chemotherapy and ICIs. The OS improved significantly in the EV cohort compared to the chemotherapy cohort (median, 12.88 months *vs.* 8.97 months, respectively; $p = 0.001$); PFS was prolonged in the EV cohort (median, 5.55 *vs.* 3.71 months; $p < 0.001$) [22]. The incidence of treatment-related AEs was comparable between the EV and chemotherapy cohorts (Table 1, Ref. [6,17–22]) [22]. The FDA granted accelerated approval of EV for patients with metastatic UC after treatment with chemotherapy and ICIs.

EV-103 is a phase Ib/II multicohort study that aims to evaluate the combination of EV and pembrolizumab in metastatic UC patients. In preliminary outcomes from a cohort of first-line cisplatin-unfit patients treated with EV and pembrolizumab, the ORR was 73.3% with a CR rate of 15.6%; the median PFS was 12.3 months. In cisplatin-ineligible patients with metastatic UC, the potential platinum-free option, EV with pembrolizumab, showed encouraging activity and durability with a manageable toxicity profile [95]. EV-302 was a phase III randomized trial that evaluated first-line EV plus pembrolizumab with chemotherapy in patients with treatment-naive advanced UC. Sacituzumab govitecan is an antibody-drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2) and SN-38 (a topoisomerase I inhibitor). As a tumor-associated calcium signal transducer 2, Trop-2 is widely expressed in UC [96]. A phase II trial examined the antitumor activity of sacituzumab govitecan in patients with metastatic UC [97]. In a preplanned interim analysis of cohort 1 (patients who progressed after prior platinum-based combination chemotherapy and ICI treatment, $n = 35$), the ORR was 29% with 2 CRs [97]. Therefore, further registration is continuing.

6. Biomarkers to predict therapeutic effects

Biomarkers are needed to predict clinical benefits that support the appropriate selection of customized therapies

for patients. Therefore, some of the most important work for developing tailored therapies is to identify baseline markers that can predict responses or toxicity [98]. Tumors with high somatic mutation rates evade immune surveillance through the dysregulation of various receptors and ligands, such as PD-1 and PD-L1 [99–101]. PD-L1 expression has been examined as a potential biomarker for the response to ICIs. In a phase I trial, PD-L1 expression on tumor cells was correlated with the response to a PD-1 inhibitor [102]. However, PD-L1 expression levels indicate heterogeneity within tumors [103], and the optimal cut-off level of PD-L1 expression is unknown [104]. In addition, some patients who do not express PD-L1 also derive a benefit from ICI treatment. For example, in the cisplatin-unfit cohort 1 of the IMvigor210 trial, PD-L1-negative patients had better OS than did PD-L1-positive patients [105]. In the KEYNOTE-052 trial, patients with a combined positive score (CPS) $\geq$10% had a higher response to pembrolizumab than did patients with CPS $<$10% [61]. However, CPS was not correlated with the tumor response in the larger KEYNOTE-045 study [19]. Because the assessment of PD-L1 expression has varied among clinical studies, a unified testing method is needed in the future. It has been hypothesized that an increased tumor mutation burden (TMB) increases the chance of producing immunogenic neoantigens [106]. Therefore, other biomarkers, such as mismatch repair (MMR) mechanisms and DNA damage response and repair (DDR) pathways are under investigation as potential biomarkers that reflect responses to ICIs in UC [107,108]. TMB refers to the total number of somatic coding mutations identified in cancer cells, indicating an MMR mechanism, tumor-infiltrating lymphocytes, a burden of neoantigens, or a lack of immune gene signatures [109]. Responses to atezolizumab were observed in all study subgroups in the IMvigor210. The tumor mutation load was significantly higher in responders than in non-responders; this correlation was observed across TCGA subtypes and PD-L1 subgroups. Patients with the highest mutation load (quartile 4) showed significant improvement of survival compared to patients in other quartiles [62]. In addition, as previously suggested, tumor mutation load, PD-L1 expression on immune cells, and tumor TCGA subtypes may be independent predictors of the therapeutic response [10]. MMR-deficient tumors respond to pembrolizumab, regardless of their origin. The FDA approved pembrolizumab for all malignant tumors with MMR defects [61,108].

There are no clinically-validated biomarkers to predict therapeutic efficacy for metastatic UC patients who receive a platinum-based regimen. A study was conducted to determine whether modifications in the genes involved in DDR are related to platinum sensitivity in patients with advanced UC [110]. In comparison to patients without DDR changes, patients with DDR changes had a prolonged PFS (median, 6.0 *vs.* 9.3 months, respectively; $p = 0.007$) and OS (median, 13.0 *vs.* 23.7 months, respectively; $p = 0.006$), suggesting that these modifications could be useful in patient selection for practice and clinical trials [110]. The inflammatory microenvironment is required for tumorigenesis because most cancers trigger an inflammatory response by establishing a pro-tumorigenic tumor microenvironment [111,112]. Potential systemic inflammatory response-related biomarkers in cancer patients are clinically known as C-reactive protein, the neutrophil-lymphocyte ratio, and albumin. Several UC studies have shown that elevated C-reactive protein levels before chemotherapy are associated with a poor prognosis [113–116]. A high neutrophil-lymphocyte ratio is associated with a poor prognosis in UC patients [117]. An association between low albumin levels and poor prognosis has been reported in UC patients [118]. These studies suggest that systemic inflammatory response-related biomarkers may be useful clinical biomarkers in UC patients. Overall, there are no definitive valid biomarkers that minimize toxicity and predict maximal therapeutic efficacy in the treatment of metastatic UC. Therefore, further research is needed to develop reliable biomarkers.

7. Conclusions

Patient factors should be considered during cancer treatment. In particular, patients with UC are often older at the time of the initial diagnosis and have several comorbidities; thus, patient factors require special consideration. ICIs have significantly improved the prognosis of patients with advanced or metastatic UC who are unfit for treatment with cisplatin-based chemotherapy. With the approval of ICIs for treatment of metastatic UC, immunotherapy has emerged as a valuable treatment option for metastatic UC in both platinum-refractory and frontline cisplatin-unfit settings. Many clinical trials are underway to determine how best to integrate immunotherapy into initial therapy and define the safety and efficacy of new immunotherapeutic drugs. Anti-angiogenics, FGFR inhibitors, and antibody-drug conjugates show considerable potential as therapeutic options for UC. Changes in the treatment paradigm and the abundance of new drugs necessitate further research and clinical trials.

Abbreviations

AE, adverse event; BSC, best supportive care; CI, confidence interval; CPS, combined positive score; CR, complete response; dd, dose-dense; DDR, DNA damage response and repair; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GC, gemcitabine, cisplatin; GCb, gemcitabine, carboplatin; HR, hazard ratio; IC, immune cell; ICI, immune checkpoint inhibitor; ITT, intention-to-treat; M-CAVI, methotrexate, carboplatin, vinblastine; MMAE, monomethyl auristatin E; MMR, mismatch repair; OS, overall survival; MVAC, methotrexate, vinblastine, adriamycin, cisplatin; NYHA, New York Heart Association; ORR, overall re-

sponse rate; PGC, paclitaxel, gemcitabine, cisplatin; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; TCGA, the Cancer Genome Atlas; TK, tyrosine kinase; TMB, tumor mutation burden; Trop-2, trophoblast cell-surface antigen 2; UC, urothelial carcinoma.

Author contributions

SHY—literature review and arrangement; SHY, HJL—writing, reviewing and approving the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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