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TOPIC PAPER

SIU-ICUD recommendations on bladder cancer: systemic therapy for metastatic bladder cancer

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Abstract
The SIU (Société Internationale d'Urologie)–ICUD (International Consultation on Urologic Diseases) working group on systemic therapy for metastatic bladder cancer has summarized the most recent findings on the aforementioned topic and came to conclusions and recommendations according to the evidence published. In Europe and the United States, treatment for metastatic UC has changed a great deal recently, mainly involving a move from chemotherapy to immune checkpoint blockers. This is particularly true in platinum-refractory disease, where supportive randomized data exist. Five checkpoint blockers have been approved in this setting by the FDA: avelumab, atezolizumab, durvalumab, nivolumab, and pembrolizumab. Nivolumab, pembrolizumab, and atezolizumab have been approved in Europe.

Keywords Bladder cancer · Urothelial cancer · Chemotherapy immunotherapy · Checkpoint inhibitors

Introduction

First-line treatment for metastatic urothelial cancer: cisplatin-eligible patients

Cisplatin-based chemotherapy was adopted as the standard of care for front-line treatment of metastatic urothelial cancer in the 1980s, when the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) demonstrated objective response rates as high as 72% in patients with metastatic incurable urothelial cancers [1]. Subsequent trials easily proved that combination cisplatin-based therapy was better than single-agent cisplatin [2]. Several decades of research into combination chemotherapy ensued; however, it soon became clear that a therapeutic plateau had been reached in clinical outcomes with combination chemotherapy that has not been surpassed in the intervening years.

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Combination cisplatin based chemotherapy

Early in the 21st Century, the doublet of gemcitabine cisplatin (GC) was accepted as a new standard of care for the treatment of patients with incurable urothelial cancers. Although the clinical trial did not meet the designed end point of an improvement in survival compared to traditional M-VAC chemotherapy, the decreased rates of neutropenia and mucositis resulted in a decreased frequency of neutropenic fever providing a less toxic alternative over traditional M-VAC chemotherapy [3]. However, it should be noted that even this new combination was toxic with only 60% of patients completing treatment on a scheduled 4-week cycle and higher rates of thrombocytopenia compared to M-VAC. As a result, many have dropped the day 15 dose of gemcitabine resulting in a more tolerable three-week combination.

Dose dense M-VAC therapy

The use of dose dense chemotherapy regimens has had a more significant impact on the toxicity of combination therapy, with only modest improvements in clinical activity. A small randomized trial of dose-dense M-VAC (DD M-VAC) was compared to the traditional 4-week cycle of M-VAC, resulting in an improved complete response rate (21% vs. 9%, $p=0.009$). Although a 50% difference in median overall survival was not detected, 2-year survival was 25% as compared to 35% with DD M-VAC and a benefit was observed in progression-free survival (unadjusted $p=0.0417$, HR = 0.76 (0.58–0.99) [4].

The improved toxicity profile with decreased rates of mucositis, neutropenia, and thrombocytopenia has resulted in the use of DD M-VAC in place of traditional M-VAC, both in the metastatic and particularly in the neoadjuvant setting with several small studies in the latter suggesting similar response rates [5–7], and long-term survival [5] as has been observed with traditional M-VAC.

Triplet chemotherapy

One might argue that the clinical trial of gemcitabine, paclitaxel, and cisplatin (GTP), was also a study of dose density. This triplet combination, given on a 3-week schedule, was compared with the 4-week schedule of the doublet combination of gemcitabine cisplatin [8]. Although this clinical trial did not meet the designed end point of improvement in survival, there were differences in toxicity with decreased frequency of thrombocytopenia and bleeding (11.4% vs. 6.8%, $p=0.0031$) and more febrile neutropenia on PCG than GC (13.2% v 4.3%, respectively; $p<0.001$).

First-line treatment for metastatic urothelial cancer: cisplatin-ineligible patients

It is estimated that approximately 50% of patients with metastatic urothelial carcinoma are ineligible for cisplatin-based chemotherapy [9]. Patients with co-morbidities tend to have worse outcomes than patients receiving cisplatin and so alternative novel therapies are very much needed for this cisplatin ineligible population. Criteria for cisplatin ineligibility are: CrCl < 60 mL/min, ECOG Performance Score 2, Grade ≥ 2 neuropathy or hearing loss and NYHA class III heart failure.

Carboplatin-based combinations

Carboplatin-based doublets have played an important role in the treatment of these patients. However, pembrolizumab (anti-PD-L1) and atezolizumab (anti-PD-1) for the front-line treatment of cisplatin-ineligible patients have become a new priority.

In an attempt to improve the toxicity profile of systemic chemotherapy, investigators have substituted carboplatin for cisplatin in several bladder regimens. An EORTC phase II/III trial compared two carboplatin-based regimens, gemcitabine and carboplatin (GCa), with methotrexate, carboplatin, and in vinblastine (MCAVI) in 238 patients who were in eligible for cisplatin-based chemotherapy [10]. In addition to poor kidney function, this trial also allowed enrollment of patients with a performance status of two. There was no difference in response, or survival when comparing GCa with MCAVI, (ORR 36.1% vs. 21.0%, $p=0.08$; median OS (overall survival) 9.3 months vs. 8.1 months, $p=0.64$). However, MCAVI had a higher rate of severe acute toxicity including death, grade 4 thrombocytopenia with bleeding, grade 3 or 4 renal toxicity, neutropenic fever, or mucositis (21.2% MCAVI vs. 9.3% GCa). In patients with both poor kidney function and poor performance status, the ORR (objective response rate) dropped and severe toxicity rates increased for both GCa and MCAVI (ORR 25% vs. 27%; severe toxicity 12.5% vs. 27.3%).

Triplet combination therapy

Triplet chemotherapy regimens have also been explored in patients with poor kidney function. A combination of gemcitabine with paclitaxel and carboplatin (GTCa) was explored in 60 patients with no or one prior chemotherapy regimen. This trial enrolled patients with both good and poor kidney function, requiring a serum creatinine ≤ 2.5 mg/dL [11]. The objective response rate was 43% with a median overall survival of 11 months. However, this regimen was

considered more toxic than was typically observed with doublet-based chemotherapy, with grade 3–4 neutropenia occurring in 72% of patients.

Front-line immunotherapy for cisplatin-ineligible patients

Immune checkpoint blockade with monoclonal antibodies directed against cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) are revolutionizing treatment paradigms across multiple cancer types. These therapies have shown striking antitumor activity in an increasing number of solid tumors and hematologic malignancies, including tumors previously not considered immune responsive. Bladder cancer, however, has long been known to be immune responsive [12]. While therapeutic cancer vaccines and anti-CTLA-4 antibodies work by priming, activating, and expanding T cells, immune checkpoint blockers such as anti-PD-1/PD-L1 antibodies restore effector T cell function against cancer cells at the tumor site [13, 14]. Hence, the PD-1/PD-L1 pathway is a powerful target for therapeutic intervention in oncology.

Two large trials of the anti−PD-1/PD-L1 agents atezolizumab and pembrolizumab for the first-line treatment of cisplatin-ineligible metastatic UC patients found these agents to be safe in this patient population [15–17]. There have also been several case reports of checkpoint blockers being safely administered to patients with end-stage renal disease on dialysis [18]. A major consideration in treating dialysis patients is the potential of anticancer drug ultrafiltration [19]. Since these monoclonal antibodies have large molecular weights, they are likely not dialyzable and may possibly be given without regard to the timing of dialysis. However, prospective trials are needed to better understand the safety profile of anti-PD-1/PD-L1 therapies in patients with significant renal impairment and end-stage renal disease and EAP (early access programs) programs are evaluating these agents in patients with poor renal function (i.e., the SAUL Study, ClinicalTrials.gov Identifier: NCT02928406).

The anti-PD-1 antibody pembrolizumab phase 2 trial, KEYNOTE-052 recruited 370 previously untreated patients who were ineligible for cisplatin-based chemotherapy [15–17]. The ORR was 29%, including 7% of patients achieving a complete response with 82% of responders maintaining their response for more than 6 months. This regimen was well tolerated with G3/4 events occurring in 19% of patients, making pembrolizumab an attractive option for cisplatin-ineligible patients. Those with a CPS $\geq$ 10% fared considerably better with a 51% RR and 18% CR rate. 82% of responders maintained a response for > 6 months.

Atezolizumab, an anti-PD-L1 antibody, was approved following a phase II trial (IMVigor210) conducted in 119 untreated patients with metastatic urothelial carcinoma who were ineligible for cisplatin due to poor kidney function, hearing impairment, or peripheral neuropathy. The objective response rate was 23%, which includes 9% of patients who experienced a complete response; 70% of responders continued to respond at a median follow-up of 1.5 years. With longer follow-up, this cohort also had a median overall survival of 15.9 months and treatment-related grade 3/4 of events in only 16% [15].

Two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130) are comparing platinum-based (including cisplatin/gemcitabine or carboplatin/gemcitabine) chemotherapy combined with pembrolizumab or atezolizumab vs. platinum-based chemotherapy alone including a third arm of monotherapy with pembrolizumab or atezolizumab to compare to platinum-based chemotherapy alone. Early reviews have found that patients in the monotherapy (pembrolizumab or atezolizumab) arms of both trials with PD-L1 low status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy. Based on these results, the US Food and Drug Administration (FDA) has restricted use to patients who are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 or for any patient ineligible for any platinum-containing therapy regardless of PD-L1 expression (https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm).

Second-line immunotherapy and chemotherapy

Immune checkpoint inhibitors in platinum-refractory urothelial cancer

In Europe and the United States, treatment for metastatic UC has changed a great deal recently, mainly involving a move from chemotherapy to immune checkpoint blockers. This is particularly true in platinum-refractory disease, where supportive randomized data exist [20, 21]. Five checkpoint blockers have been approved in this setting by the FDA: avelumab, atezolizumab, durvalumab, nivolumab, and pembrolizumab [20–25]. Nivolumab, pembrolizumab, and atezolizumab have been approved in Europe (source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003985/human_med_001876.jsp&mid=WC0b01ac058001d124). These approvals are not all based on randomized phase III trials. Indeed, two approvals were based on large phase I/II trials in the US. This unusual occurrence reflects the current enthusiasm for treating patients with these agents in the clinical setting and is driven by the modest proportion of patients who achieve long-term, well-tolerated durable benefit. One of the complicating features of these studies is the selection of patients for treatment, which has at times been based on the PD-L1 biomarker [13].

Randomized phase III data on platinum-refractory UC

The KEYNOTE-045 and IMvigor211 trials studied pembrolizumab and atezolizumab, respectively, in patients who had progressed after 1–2 lines of chemotherapy [13, 14] (Table 1). The study drugs were compared to chemotherapy, for which investigators were given a choice between taxanes and vinflunine due to the lack of a global standard of care. The major difference between the two trials was their primary end points: for pembrolizumab, overall survival (OS) in the intention-to-treat (ITT) population; for atezolizumab, OS in the PD-L1-positive population (SP142 antibody > 5% of immune cells staining positive).

KEYNOTE-045 was an open-label, international phase 3 trial that demonstrated an improvement in survival in patients with advanced urothelial carcinoma with the anti-PD-1 antibody, pembrolizumab compared to investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) [14]. In the control arm ($n = 272$), 168 patients received taxanes (84 docetaxel, 84 paclitaxel) and 87 received vinflunine. Response rates (21%) were significantly higher with pembrolizumab. Moreover, duration of response was longer with immunotherapy. Progression-free survival (PFS) was similar in both arms. Data on toxicity and quality of life clearly supported pembrolizumab. The median overall survival in all patients was 10.3 months (95% CI, 8.0–11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI, 6.1–8.3) in the chemotherapy group (HR, 0.73; 95% CI, 0.59–0.91; $p = 0.002$). The median overall survival among patients who had a tumor and tumor associated immune cells PD-L1 combined positive score of 10% or more was 8.0 months (95% CI, 5.0–12.3) in the pembrolizumab group, as compared with 5.2 months (95% CI, 4.0–7.4) in the chemotherapy group (HR, 0.57; 95% CI, 0.37–0.88; $p = 0.005$).

Fewer treatment-related adverse events of any grade were reported in the pembrolizumab group than in the chemotherapy group (60.9% vs. 90.2%); there were also fewer events of grade 3, 4, or 5 severities reported in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4%). An updated analysis with 27.7 months median follow-up reported a median OS of 10.3 months for pembrolizumab compared to 7.3 months for chemotherapy.

Estimated OS at 24 months was 27% for pembrolizumab vs. 14.3% for chemotherapy [26]. These data, the most robust for any of the checkpoint blockers in this setting, are practice changing. The PD-L1 biomarker results (22C3 antibody with combined immune and tumor-component staining) were more controversial. Although results showed enrichment with pembrolizumab (0.57; 95% CI 0.37–0.88), they did not meet predefined statistical endpoints. Sensitivity and specificity of this biomarker are not high enough to conclude on the benefits of therapy based on PD-L1-biomarker status.

The second-phase III trial in patients with platinum-resistant metastatic urothelial cancer is IMvigor 211, was a larger study that enrolled 931 patients and randomized patients 1:1 to atezolizumab vs. investigator's choice chemotherapy (paclitaxel, docetaxel, or vinflunine). Patients with metastatic urothelial carcinoma who had progressed after platinum-based chemotherapy were randomly assigned (1:1), to receive atezolizumab 1200 mg or chemotherapy (physician's choice: vinflunine 320 mg/m(2), paclitaxel 175 mg/m(2), or 75 mg/m(2) docetaxel) intravenously every 3 weeks. Randomisation was stratified by PD-L1 expression (expression on < 1% [IC0] or 1% to < 5% [IC1] of tumor-infiltrating immune cells vs. ≥ 5% of tumor-infiltrating immune cells [IC2/3]), chemotherapy type (vinflunine vs.

Table 1 Summary of randomized phase III trials in platinum-refractory UC

Study drug	KEYNOTE-045 Pembrolizumab	IMvigor211 Atezolizumab
Number of patients receiving study drug	270	467
PS 2	1%	0
Bladder primary	86%	69%
Patients with ≥ 2 risk factors	41%	23%
Visceral metastasis	89%	77%
Liver metastasis	34%	30%
≥ 2 previous lines of therapy	20%	19%
Vinflunine in control arm	34%	54%
PD-L1-positive patients	40%	25%
Response rate in ITT	21%	13%
OS in PD-L1-positive patients	0.59 (95% CI 0.37–0.88)	0.87 (95% CI 0.62–1.21)
Response rate in PD-L1-positive patients	22%	23%
Overall survival in all patients	0.73 (95% CI 0.59–0.91)	0.85 (95% CI 0.71–0.99)

taxanes), liver metastases (yes vs. no), and number of prognostic factors (none vs. one, two, or three). The primary endpoint of overall survival was tested hierarchically in prespecified populations: IC2/3, followed by IC1/2/3, followed by the intention-to-treat population.

In the IC2/3 population ($n = 234$), overall survival did not differ significantly between patients in the atezolizumab group and those in the chemotherapy group (median 11.1 months [95% CI 8.6–15.5; $n = 116$] vs. 10.6 months [8.4–12.2; $n = 118$]; stratified hazard ratio [HR] 0.87, 95% CI 0.63–1.21; $p = 0.41$), thus precluding further formal statistical analysis.

Duration of response was numerically longer in the atezolizumab group than in the chemotherapy group (median 15.9 months [95% CI 10.4 to not estimable] vs. 8.3 months [5.6–13.2]; HR 0.57, 95% CI 0.26–1.26).

Atezolizumab was not associated with significantly longer overall survival than chemotherapy in patients with platinum-refractory metastatic urothelial carcinoma overexpressing PD-L1 (IC2/3). However, the safety profile for atezolizumab was favorable compared with chemotherapy; exploratory analysis of the intention-to-treat population showed well-tolerated, durable responses in line with previous phase 2 data for atezolizumab in this setting [13]. Together, these results showed that the PD-L1 biomarker selected responders to both immunotherapy and chemotherapy. The biomarker endpoint was chosen because of impressive results in the phase I and II trials. However, these single-arm studies were not able to distinguish between the prognostic and predictive factors of the biomarker. IMvigor211 highlights the risks of biomarker-driven approaches. Statistical significance cannot be drawn from the ITT population due to the study design.

These studies provide further evidence for the modest, yet variable, activity of chemotherapy in the second-line setting and argue strongly for continued investigation of novel therapies in those patients who do not respond or progress after immune checkpoint blockade [13].

Phase I and II trials for durvalumab, avelumab, and nivolumab

There are no randomized data on durvalumab, avelumab, or nivolumab in platinum-refractory disease. All three agents have been given FDA approval (https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm539646.htm) based on phase I or II data [22–24]. The majority of phase II data for atezolizumab came from IMvigor210. This drug was the first to show high response rates, impressive landmark survival, and biomarker enrichment for response [25]. The randomized phase III data described above have superseded this study.

It is noteworthy that each of the five checkpoint blockers employed a unique method of biomarker analysis. Also, some of the trials described below had enrichment phases, where only biomarker-positive patients were enrolled. Therefore, any form of cross-trial comparison is futile.

An overview of the agents with no randomized data in this setting underlines the consistency of the results. Nivolumab has both FDA and EMA approval. It was tested in a phase II study with 270 patients [22]. Response rates were 19.6% (15.0–24.9%), and median OS was 8.7 months (6.1–NA). PD-L1 positivity was defined as > 1% expression on tumor cells. Inconsistencies occurred with this biomarker. Durvalumab was tested in 191 patients. Response rates were 18%, and OS was 18.2 months (95% CI 8.1–NA), although the analysis was performed with a median follow-up of 5.8 months [24]. Biomarker-positive patients (SP263-positive in immune and tumor cells) had better outcomes. A degree of patient selection occurred in this study due to biomarker enrichment. Avelumab was tested in 44 patients [23]. Response rates were 18.2%, and median OS was 13.7 months (95% CI 8.5–NA). Conclusions to be drawn from these three studies include: (a) A proportion of patients achieve long-term durable benefit with each of the drugs, usually between a fifth and a third of patients, depending on biomarker enrichment. (b) The agents appear to be well tolerated, with similar adverse-event profiles. (c) Inconsistent results have been seen with the biomarker across the board. This has hampered development of the drugs and none of the agents has biomarker-driven regulatory approval. (d) A majority of patients get no significant long-term benefit from these agents. Median PFS is always short, and disease progression is most common as a best response to therapy in this setting. This is particularly true for patients with liver metastasis.

These results elicit key questions concerning the next steps in this area of high unmet need. Can efficacy be improved? New combinations are needed to increase response rates and outcomes. These may or may not be immune/immune combinations, as chemotherapy and targeted therapy combinations hold promise as well. The next question is what can be done to better identify patients who have clear benefit. There is a need to find alternative biomarkers to PD-L1. Tumor mutational burden and immune gene signatures have been investigated with some success. Finally, should we be testing these drugs earlier in the disease setting? A plethora of front-line trials and studies in earlier disease states are ongoing [27]. These trials combine immunotherapy with combination chemotherapy or immunotherapy alone. As mentioned earlier, two of the trials have recently been halted and only patients whose tumors or immune cells express PDL-1 will be randomized. The FDA on the 25th of May warned oncologists and clinical trial investigators of early signs from two trials that some

bladder cancer patients treated first with either pembrolizumab Keytruda or atezolizumab Tecentriq alone were dying sooner than those given platinum-based chemotherapy. Reviews by data monitoring committees overseeing KEYNOTE-361 and IMvigor130 observed decreased survival in the monotherapy arm of each study among patients whose tumors expressed low levels of PD-L1. These data illustrate the difficulties in interpreting and utilizing the results of the PD-L1 biomarker assay.

Summary

Immunotherapy has been shown to be highly effective following platinum-based chemotherapy in approximately 20–25% of patients and in patients who are ineligible for platinum-based chemotherapy. Unfortunately, despite the enthusiasm, only few patients are actually benefiting from anti-PD-1/PD-L1 therapy, a situation that calls for further intensive study and other novel therapies. Although phase II data show similarities across the board for these agents, both positive and negative randomized data exist, highlighting the need to identify better combination treatments and biomarkers.

Chemotherapy

Vinflunine, a microtubule inhibiting vinca alkaloid, has been investigated in the second-line setting. A randomized phase III trial accrued 370 patients and compared vinflunine plus best supportive care (BSC) to BSC alone as second-line therapy [28]. Patients progressing after front-line platinum-containing chemotherapy for metastatic disease were included, and those who had received prior peri-operative chemotherapy only were excluded. An improvement in survival, the primary endpoint, was not demonstrated by an intention-to-treat (ITT) analysis (6.9 vs. 4.6 months, $p = 0.287$), but there was a statistical improvement in RR (8.6 vs. 0%) and median progression-free survival (PFS) (3.0 vs. 1.5 months). In another analysis of only the eligible patient population ($n = 357$), the median survival was significantly longer for vinflunine + BSC compared to BSC alone (6.9 vs. 4.3 months, $p = 0.04$). Based on this study, vinflunine was approved by the EMA, but not by the FDA. Vinflunine has also been investigated as maintenance strategy after first-line therapy in patients with advanced urothelial carcinoma [29]. A multicenter open-label, randomized phase 2 trial of maintenance therapy with vinflunine plus BSC vs. BSC alone in 88 patients demonstrated an improvement in PFS with vinflunine plus BSC (median PFS was 6.5 months [95% CI 2.0–11.1] in the vinflunine group and 4.2 months [95% CI 2.1–6.3] in the BSC group [HR 0.59, 95% CI 0.37–0.96, $p = 0.031$]). Overall, vinflunine has limited activity in patients with metastatic urothelial carcinoma. An OS benefit was seen in the randomized phase 3 trial as compared to BSC in the eligible patient population but not by ITT analysis (LE 2, GR B) [28].

Taxanes (paclitaxel, docetaxel, nanoparticle-albumin-bound paclitaxel) have been evaluated following first-line GC, while gemcitabine and the taxanes, alone or in combination have been employed following M-VAC. Both docetaxel and paclitaxel have demonstrated modest RRs (10–15%) and poor survival outcomes (6–9 months) [30, 31]. In spite of poor patient outcomes, in the absence of alternative therapies, taxanes have been a mainstay of treatment for patients who had progressed after platinum-based chemotherapy until the recent approval of immune checkpoint inhibitors in the second-line setting. Somewhat ironically, the control arms from the recently reported randomized phase 3 trials comparing immune checkpoint blockade with chemotherapy in patients with platinum-resistant metastatic urothelial cancer provide the largest prospective datasets of second-line chemotherapy to date [20, 32]. Overall, taxanes appear to have limited activity in patients with metastatic urothelial carcinoma as second-line therapy and with the more recent FDA https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555930.htm) approval of five immune checkpoint inhibitors in platinum pre-treated patients, taxane use has an even more limited role in the salvage setting (LE 2, GR B). Other agents that have been evaluated in the second-line setting are found in Table 2. There is also no clear role for single-agent VEGF receptor tyrosine kinase inhibitors in the management of patients with metastatic urothelial carcinoma (LE 2, GR B).

Combination chemotherapy

Combination chemotherapy regimens have been evaluated as second-line therapy in phase II trials. A German randomized phase 3 trial of 102 patients compared the strategy of six cycles of second-line gemcitabine-paclitaxel with continuation beyond six cycles until progression [33]. None of the patients had received previous paclitaxel, and approximately half had received prior gemcitabine. The median OS was 7–8 months and the median PFS was approximately 3–4 months in both groups. The strategy of a fixed number of cycles vs. continuation until disease progression could not be evaluated since a mean of only four cycles was delivered in both groups due to rapid tumor progression and toxicity.

Another trial evaluated carboplatin–paclitaxel following prior cisplatin-based chemotherapy not including paclitaxel, and reported an RR of 16%, median PFS of 4 months and median survival of 6 months [34]. A phase I/II trial evaluated a combination of salvage weekly cisplatin, gemcitabine and ifosfamide in a heterogeneous group of patients that had received previous platinum-based

Table 2 Selected phase II trials of second-line chemotherapy and VEGF-targeted therapy for metastatic urothelial carcinoma

Drug	*n*	RR (%)	PFS (mo)	OS (mo)
Ifosfamide [46]	56	20	2.4	5.5
Gemcitabine [47]	30	11	4.9	8.7
Gemcitabine [48]	35	22.5	–	5.0
Weekly paclitaxel [31]	31	10	2.2	7.2
Docetaxel [30]	30	13	–	9.0
Nab-paclitaxel vs. paclitaxel	199	21 vs. 23	−3.35 vs. 3.02	−7.46 vs. 8.77
Paclitaxel–gemcitabine [49]	41	60	–	14.4
Ifosfamide–gemcitabine [50]	34	21	4.0	9.0
Carboplatin–paclitaxel [34]	44	16	4.0	6.0
Pemetrexed [51]	47	27.7	2.9	9.6
Pemetrexed [52]	12	8	–	–
Ixabepilone [53]	42	11.9	2.7	8.0
Oxaliplatin [54]	18	6	1.5	7.0
Vinflunine [55]	175	15	2.8	8.2
Vinflunine [56]	51	18	3.0	6.6
Irinotecan [57]	40	5	2.1	5.4
Topotecan [58]	44	9.1	1.5	6.3
Sorafenib [59]	27	0	–	6.8
Sunitinib [60]	45	7	2.4	6.9
Pazopanib [61]	41	17.1	2.6	4.7
Pazopanib [62]	19	0	1.9	–
Pazopanib [63]	66	4.5	3.1	4.7
Docetaxel–ramucirumab [44]	46	24	5.4	10.4

NA not available or stipulated in publication, *VEGF* vascular endothelial growth factor

chemotherapy [35]. The RR was 40.8% but hematologic toxicities appeared prohibitive. Similarly, the combination of pemetrexed and gemcitabine has demonstrated moderate activity coupled with substantial myelosuppression [36, 37]. Scant data support re-administration of second-line M-VAC following prior first-line M-VAC in those patients with an excellent previous quality of response and relatively prolonged time to progression [38]. Limited retrospective data suggest that M-VAC may have activity after GC and GC may have activity after M-VAC [39, 40].

Pooled data from salvage systemic therapy phase 2 trials have suggested a benefit for combination chemotherapy as compared to single-agent therapy. An analysis of individual patient level data from eight phase 2 trials of single-agent taxane vs. taxane containing combination chemotherapy in 370 patients demonstrated that combination chemotherapy was independently and significantly associated with improved OS (HR: 0.60; 95% CI, 0.45–0.82; $p = 0.001$) [41]. In contrast to this finding, a systematic review and meta-analysis evaluated single-agent or doublet chemotherapy in the second-line setting after platinum-based chemotherapy including 46 arms of trials including 1910 patients: 22 arms with single agent ($n = 1202$) and 24 arms with doublets ($n = 708$) [42]. Despite significant improvements in ORR and PFS, doublet regimens did not extend OS compared with single agents for the second-line chemotherapy of UC.

There is no clear benefit for the use of combination chemotherapy over single-agent chemotherapy in the salvage treatment of patients with metastatic urothelial cancer (LE 2, GR B).

The use of VEGF receptor tyrosine kinase inhibitors such as sunitinib in combination with chemotherapy has proved challenging due to poor tolerability [43]. A recently reported open-label, three-arm, randomized phase 2 trial in the second-line treatment of locally advanced or metastatic urothelial carcinoma compared docetaxel monotherapy with docetaxel combined with ramucirumab, a VEGF receptor two antibody and docetaxel combined with icrucumab, a VEGF receptor one antibody [44]. The addition of ramucirumab to docetaxel resulted in an improvement in PFS compared with docetaxel monotherapy (median, 5.4 months; 95% CI, 3.1–6.9 months vs. 2.8 months; 95% CI, 1.9–3.6 months; stratified hazard ratio, 0.389; 95% CI, 0.235–0.643; $p = 0.0002$). There was no benefit associated with the addition of icrucumab. The phase 3 RANGE trial randomized 530 patients with locally advanced or unresectable or metastatic urothelial carcinoma whose disease progressed on or after platinum-based chemotherapy to docetaxel plus either ramucirumab ($n = 263$) or placebo ($n = 267$) with a primary

endpoint of PFS [45]. PFS was prolonged significantly in patients allocated ramucirumab plus docetaxel vs. placebo plus docetaxel (median 4.07 months [95% CI 2.96–4.47] vs. 2.76 months [2.60–2.96]; hazard ratio [HR] 0.757, 95% CI 0.607–0.943; $p = 0{\cdot}0118$). Ramucirumab plus docetaxel is the first regimen in a phase 3 study to show superior PFS compared to chemotherapy in patients with platinum-refractory advanced urothelial carcinoma. OS data are anticipated. No formal recommendation for the use of ramucirumab in combination with docetaxel can be made yet at this time.

Level of evidence and grades of recommendation for second-line and salvage chemotherapy

With the recent approval of five immune checkpoint inhibitors in the treatment of patients with metastatic urothelial carcinoma who have progressed after platinum-based chemotherapy, in the great majority of patients, the use of chemotherapy should be considered only after a trial of immune checkpoint blockade. Single-agent chemotherapy including vinflunine, paclitaxel and docetaxel has very limited activity in the salvage setting (LE 2, GR B). There is no clear role for the use of combination chemotherapy over single-agent chemotherapy in the salvage setting (LE 2, GR B). Although promising data exist for the combination of ramucirumab and docetaxel, no formal recommendation for the combination can be made at this time.

Summary and recommendations

Front-line—cisplatin-eligible

- Front-line treatment for patients with unresectable or metastatic urothelial carcinoma of the bladder should consist of combination cisplatin-based chemotherapy. The cisplatin-based regimen can be M-VAC, DD M-VAC, or GC. (LOE 1, Grade A).
- Bajorin risk stratification can be employed in cisplatin-eligible patients with metastatic urothelial cancer (LOE 2, Grade B).

Front-line—cisplatin-ineligible

- In patients with renal impairment, advanced age or poor performance status, carboplatin and gemcitabine is recommended for front-line therapy (LOE 2, Grade B).
- The addition of paclitaxel or other agents to gemcitabine plus cisplatin or to gemcitabine plus carboplatin in cisplatin-ineligible patients is not recommended (LOE 2, Grade C).
- Immunotherapy with pembrolizumab or atezolizumab can be considered in the front-line setting in cisplatin-ineligible patients and PD-L1 positive tumor based on single-arm, phase II trials (LOE 2, Grade C).

Second-line chemotherapy

- Risk stratification of patients in the second-line setting can be based on ECOG performance status (PS > 1), hemoglobin level (< 10 g/dL), presence of liver metastases, and time from previous chemotherapy (LOE 2, Grade B).
- The administration of chemotherapy in the second-line setting will depend on the patient's performance status, co-morbidities and age. The decision to treat will also depend on the patient's willingness to receive chemotherapy (LOE 2, Grade B).
- Only marginal benefit is expected from standard chemotherapy in patients with poor PS (> 1). Therefore, the best supportive care should be considered in these patients (LOE 3, Grade C).
- If the renal function is adequate and progression occurs > 6 months after first-line therapy and patients present with PS = 0 or 1, re-exposure to first-line cisplatin-based treatment can be considered (LOE 3, Grade B).
- Vinflunine is approved for second-line therapy after platinum-based therapy in Europe but not in North America. Where available, it should be considered for second-line chemotherapy after prior platinum-based therapy (LOE 2, Grade B).
- Mono- or combination chemotherapy especially with paclitaxel, docetaxel, pemetrexed, gemcitabine and carboplatin may be considered in the second line (LOE 3, Grade B).

Second-line immunotherapy

- Anti-PD-1/PD-L1 checkpoint blockade demonstrates improved objective response rates and overall survival with less toxicity compared to second-line single-agent chemotherapy after prior platinum-based therapy. The level of evidence for superiority of checkpoint blockade over chemotherapy is highest for pembrolizumab. These agents should, therefore, be preferred over chemotherapy in this setting (LOE 2, Grade B).
- PD-L1 expression by immunohistochemistry is inadequate to predict response to anti-PD-1/PD-L1 checkpoint inhibitors (LOE 2, Grade D).
- There is insufficient evidence to support the use of total mutational burden to predict response to anti-PD-1/PD-L1 checkpoint inhibitors (LOE 2, Grade D).

Targeted therapy

- Novel targeted therapies for urothelial cancer are urgently needed (Grade C).

Author contributions All authors contribute to protocol/project development, data collection or management, data analysis and manuscript writing/editing

Compliance with ethical standards

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