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Upper tract urothelial carcinoma topical issue 2016: treatment of metastatic cancer

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Abstract

Purpose—To review the management of metastatic upper tract urothelial carcinoma (UTUC) including recent advances in targeted and immune therapies as an update to the 2014 joint international consultation on UTUC, cosponsored by the Société Internationale d'Urologie and International Consultation on Urological Diseases.

Methods—A PubMed database search was performed between January 2013 and May 2016 related to the treatment of metastatic UTUC, and 54 studies were selected for inclusion.

Results—The management of patients with metastatic UTUC is primarily an extrapolation from evidence guiding the management of metastatic urothelial carcinoma of the bladder. The first-line therapy for metastatic UTUC is platinum-based combination chemotherapy. Standard second-line therapies are limited and ineffective. Patients with UTUC who progress following platinum-based chemotherapy are encouraged to participate in clinical trials. Recent advances in genomic profiling present exciting opportunities to guide the use of targeted therapy. Immunotherapy with checkpoint inhibitors has demonstrated extremely promising results. Retrospective studies provide support for post-chemotherapy surgery in appropriately selected patients.

Conclusions—The management of metastatic UTUC requires a multi-disciplinary approach. New insights from genomic profiling using targeted therapies, novel immunotherapies, and surgery represent promising avenues for further therapeutic exploration.

Keywords

Upper tract urothelial carcinoma (UTUC); Chemotherapy; Targeted therapy; Immunotherapy; Anti-PD-1; Anti-PD-Ll; Immune checkpoint inhibitors

Introduction

Although the management of metastatic upper tract urothelial carcinoma (UTUC) is generally extrapolated from the treatment of metastatic urothelial carcinoma of the bladder (UCB), distinct clinical and biological features of UTUC raise important questions regarding the appropriateness of this approach. Importantly, the majority of patients with metastatic UTUC have renal dysfunction that may result from a solitary kidney, tumor infiltrating the kidney, or hydronephrosis from urinary obstruction, impacting treatment options. Specifically, patients with metastatic UTUC may be at increased risk for chemotherapy-induced nephrotoxicity with cisplatin-based chemotherapy. Unfortunately with UTUC comprising only 8–10 % of all urothelial carcinomas (UC), patients with UTUC and UCB are often combined in clinical trials that frequently neglect to stratify by primary site. There are limited data specific to the management of metastatic UTUC, and dedicated clinical trials are needed.

Methods

An international, multi-disciplinary committee of experts previously reviewed the management of metastatic UTUC at the Société Internationale d'Urologie (SIU) conference held in September 2013. Their overview was published in 2014 in the joint consultation on UTUC, co-sponsored by the SIU and International Consultation on Urological Diseases (ICUD) [1]. To update this previous analysis, a Pub-Med database search was performed to review studies published between January 2013 and May 2016 related to the treatment of metastatic UC, including UTUC. Titles and/ or abstracts were initially assessed for relevance to topics including first-line chemotherapy in cisplatin-eligible and ineligible patients, second-line chemotherapy, genomic profiling and targeted therapy, immunotherapy, and surgery, including post-chemotherapy lymphadenectomy and visceral metastasectomy. For pertinent articles, the full text was analyzed for key contributions related to the topics. Thirteen medical oncologists and urologists, all of whom previously contributed to the original review, evaluated the analysis for accuracy and inclusion and exclusion of studies. A total of 54 studies were selected for inclusion in the update. Outcomes reported for studies evaluating first-line and second-line therapies for metastatic UC, including UTUC, are presented in Table 1. Table 2 provides a summary of planned, ongoing, and recently completed trials.

Results

First-line chemotherapy in cisplatin-eligible patients

Similar to patients with UCB, the first-line treatment for metastatic UTUC is cisplatin-based combination chemotherapy; however, an initial determination must be made regarding "fitness" for cisplatin. Using a consensus definition, patients meeting any of the following criteria are considered unfit for cisplatin: (1) World Health Organization (WHO) or Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 or Karnofsky performance status (KPS) ≤ 60–70 %; (2) creatinine clearance (CrCl) < 60 mL/min; (3) grade ≥ 2 hearing loss; (4) grade ≥ 2 peripheral neuropathy; and (5) New York Heart Association (NYHA) class ≥ III heart failure [2]. For cis-platin-eligible patients, three standard regimens may be considered for the first-line treatment of metastatic UTUC: methotrexate, vinblastine, doxorubicin, plus cisplatin (MVAC); dose-dense MVAC (DD-MVAC); and gemcitabine plus cisplatin (GC).

MVAC became the first primary regimen for metastatic UC after demonstrating a median survival of 13 months in spite of significant toxicity including myelosuppression, mucositis, and drug-related mortality in 3–4 % of patients [3, 4]. The introduction of granulocyte colony-stimulating factor (G-CSF) decreased the incidence of myelosuppression and mucositis. DD-MVAC with G-CSF support as compared to MVAC demonstrated similar survival outcomes in an initial analysis [5] and higher 5-year survival after a median follow-up of 7.3 years (21.8 vs. 13.5 %; $p = 0.042$) [6].

In 2000, the combination of GC was shown to be better tolerated than MVAC with comparable efficacy. A randomized phase III trial revealed similar overall survival (OS) (13.8 months with GC vs. 14.8 months with MVAC; $p = 0.75$) with patients receiving GC

experiencing improvement in performance status (PS), weight, and fatigue [7]. GC was associated with increased thrombocytopenia, yet had reduced febrile neutropenia, neutropenic sepsis, mucositis, and lower drug-related mortality (1 vs. 3 %). Given these results, GC became the standard first- line chemotherapy for patients with metastatic UC including those with UTUC fit for cisplatin-based combination chemotherapy.

Until very recently, there had been three decades of no major advances in the treatment of metastatic UC. For example, taxane-based doublets did not improve upon established treatments. A phase III trial compared paclitaxel plus carboplatin to classic MVAC but was terminated early due to slow accrual, limiting conclusions [8]. Compared to docetaxel plus cisplatin, DD-MVAC had a superior median survival of 14.2 months (vs. 9.3 months); however, after adjusting for prognostic factors, the survival difference became nonsignificant [9].

Another study comparing dose-dense GC to DD-MVAC demonstrated that dose-dense GC was not superior but better tolerated [10]. Once again, the trial was fraught with slow accrual and consequently had a small sample size, limiting the impact of its findings. Many have attempted to enhance the efficacy of GC with an additional agent. In a phase III EORTC trial, the addition of paclitaxel (PGC) did not significantly improve survival compared to GC (15.8 vs. 12.7 months; $p = 0.075$) [11]. Neutropenic fever was also more common with PGC. More recent attempts at improving upon GC incorporate targeted therapies. Vascular endothelial growth factor (VEGF) inhibitors such as sunitinib and sorafenib have been evaluated in triplet regimens with GC as the backbone; however, these combinations have not improved efficacy (Table 1) [12, 13].

In conclusion, MVAC, DD-MVAC, and GC are the most effective regimens for metastatic UC. Since the majority of patients in these trials had metastatic UCB, the treatment of metastatic UTUC with these regimens in practice represents an extrapolation of these data.

First-line chemotherapy in cisplatin-ineligible patients

The major comorbidity limiting cisplatin administration in metastatic UTUC is poor renal function related to a solitary kidney. Undergoing a nephroureterectomy increases the likelihood of ineligibility for cisplatin. Using a cutoff estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2, one retrospective review of 388 patients with UTUC undergoing a nephroureterectomy found that while 49 % were eligible for cisplatin preoperatively, only 19 % were eligible postoperatively [14]. The decline in function failed to recover 5 months after surgery [15].

In 2012, the EORTC reported the first large randomized phase II/III study of cisplatin-ineligible patients with advanced UC [16]. Criteria defining cisplatin-ineligibility were a WHO PS of 2 and/or GFR of < 60 but > 30 ml/ min. The study compared carboplatin plus gemcitabine (carbo/gem) to methotrexate, carboplatin, plus vinblastine (M-CAVI). Carbo/gem and M-CAVI had comparable median OS (9.3 vs. 8.1 months; $p = 0.64$), but carbo/ gem had less severe acute toxicity (9 vs. 21 %). UTUC accounted for 20 and 24 % of each arm, respectively, but outcomes were not stratified by primary site. Owing to its better toxicity profile, carbo/gem is the favored regimen for cisplatin-ineligible patients.

Triplet therapy with a carbo/gem backbone has also been investigated. A phase II trial evaluated bevacizumab plus carbo/gem in 51 chemotherapy-naive patients with a calculated CrCl of < 60 but ≥ 30 mL/min (76 % of patients), solitary kidney (29 %), KPS of 60–70 % (8 %), or visceral metastases (53 %) [17]. UTUC comprised 39 % of patients. Although the trial did not meet its primary endpoint of progression-free survival (PFS) of > 4.8 months, the median OS was promising at 13.9 versus 10.3 months in a historical control receiving carbo/gem. On univariate analysis, primary site was not significantly associated with outcome. Treatment was reasonably well tolerated compared to the historical control. A phase III National Cancer Institute cooperative group study evaluating bevacizumab plus GC instead of carbo/gem has been completed with no results to date (NCT00942331).

Several studies have modified conventional GC by delivering weekly cisplatin 35 mg/m^2 in patients with impaired renal function. A phase I/II trial evaluated GC with gemcitabine 1000–1100 mg/m^2 and cisplatin 35 mg/m^2 both delivered on days 1 and 8 every 21 days [18]. Of 32 patients, 19 had a GFR < 60 ml/min but > 40 ml/min. The median OS was 16 months, and no clinically significant decline in renal function was reported. Morales-Barrera and colleagues reported outcomes for 38 patients with a CrCl between 35 and 59 ml/min treated with gemcitabine 2500 mg/m^2 and cisplatin 35 mg/m^2 on days 1 and 15 every 28 days [19]. The median OS was 8.5 months. A phase II/ III trial comparing fractionated GC to carbo/gem is currently enrolling patients (NCT02240017).

Vinflunine is an agent unavailable in the USA but approved for use in certain European countries, among others. A randomized phase II trial of 69 cisplatin-ineligible patients with locally advanced or metastatic UC compared vinflunine–gemcitabine (VG) to vinflunine–carboplatin (VC) [20]. All patients had a PS of 0 or 1 and were cisplatin-ineligible based on calculated CrCl < 60 but ≥ 30 mL/min and/or NYHA class II/III heart failure. UTUC accounted for 50 % of VG and 43 % of VC cases. The median OS for VG and VC was 14.0 and 12.8 months, respectively ($p = 0.860$). Survival outcome was not stratified by primary site. VG was associated with less grade 3/4 neutropenia (38 vs. 68 %; $p = 0.028$) and less grade 3/4 thrombocytopenia (6 vs. 21 %). Overall, the trial favored VG, which showed similar survival and less hematologic toxicity compared to VC and historical carbo/gem rates.

In conclusion, the first-line standard therapy for cis-platin-ineligible patients is carbo/gem. Carbo/gem has comparable survival and is better tolerated than M-CAVI. Carbo/gem plus bevacizumab and VG also demonstrate potential in cisplatin-ineligible patients, warranting further evaluation.

Second-line therapy for metastatic UC

No standard therapy exists for patients who progress following first-line platinum-based chemotherapy. Where available, vinflunine may be used, albeit with limited efficacy. In this setting, vinflunine with best supportive care (BSC) versus BSC alone did not significantly improve survival in the intention-to-treat population in a randomized phase III trial [21]. That being said, on multivariate Cox analysis, the improvement was significant after adjusting for “eligible” patients (6.9 vs 4.3 months; $p = 0.040$). On account of this survival

benefit, the European Medicines Agency approved vinflunine for use in the second-line setting for metastatic UC.

Several agents have been studied in phase II trials for pre-treated metastatic UC. Paclitaxel, docetaxel, and peme-trexed are commonly used and have reasonable tolerability with a median OS ranging from 7 to 10 months (Table 1) [22–24]. PFS and response rates are poor. The addition of a VEGF inhibitor ramucirumab to docetaxel in platinum-refractory UC improved PFS in a phase II trial (5.4 vs 2.8 months; $p = 0.0002$) [25]. Although doublet therapy did not improve median OS, the trial met its pre-specified efficacy endpoint and an ongoing phase III trial is underway (NCT02426125). Given the absence of approved, effective therapies for patients who progress following platinum-based chemotherapy, enrollment on a clinical trial is the preferred strategy (Table 2).

Advances in UC biology lead to novel therapeutic strategies

For the past three decades, no significant breakthroughs have occurred in the management of metastatic UC since the arrival of MVAC, calling for a strategic shift toward novel approaches based on recent advances in the understanding of UC biology. Recently, the Cancer Genome Atlas (TCGA) identified molecular alterations in UC that have opened the doors for novel therapeutic approaches [26]. Potential therapeutic targets were present in 69 % of tumors analyzed. Specific molecular alterations included those involved in the RTK/Ras/PI(3)K, cell-cycle regulation and chromatin-remodeling pathways. For example, common alterations included *PIK3CA* and *AKT3* in the PI(3)K/AKT/mTOR pathway and *FGFR3* and *ERBB2* in the RTK/RAS pathway, all of which have either targeted therapies approved or under investigation [27]. In one published report, a patient with metastatic UCB progressed after 4 cycles of MVAC and showed further progression following salvage chemotherapy with two cytotoxic regimens [28]. Genomic profiling of the tumor revealed an *FGFR3* activating mutation and amplification. Pazopanib, a multi-kinase inhibitor with targets including FGFR, induced a durable partial response (PR) in spite of a previous phase II study of pazopanib in metastatic UC with no objective response in 16 patients [29]. Similarly, a case of platinum and taxane-refractory advanced UC experienced a durable response with a combination of pazopanib and everolimus in a phase I trial [30]. Whole-exome sequencing revealed two activating *mTOR* mutations. These cases highlight the potential benefit of using genomic interrogation to guide targeted therapy.

Gene expression profiling by several groups has also suggested there are intrinsic subtypes of UCB that may differ in their underlying biology and overall prognosis [26, 31, 32]. Recent data suggest that these subtypes may predict for benefit from chemotherapy and immunotherapy [33, 34]. The luminal subtype appears enriched for FGFR mutations [26, 31, 32]. This likely reflects a difference in the underlying biology of UTUC, since luminal subtype [33] and FGFR mutations [35] have been reported to occur with higher frequency in these patients.

In 2015, Sfakianos and colleagues reported the most comprehensive genomic profiling of UTUC to date by sequencing protein-coding exons of 300 genes, including those frequently mutated in the TCGA analysis of UCB, and comparing the results to those of concomitantly analyzed UCB tumors [35]. Broadly, high-grade UTUC and high-grade UCB shared

tendencies in the specific genes altered, but the frequencies of these genetic alterations differed significantly. Similar to UCB, UTUC harbored alterations in *FGFR3*, chromatin-modifying genes, *HRAS,* and *TP53.* In UTUC tumors, however, *HRAS* and *CDKN2B* were more frequently mutated *(HRAS:* 14 vs. 1 %, $p = 0.001$; *CDKN2B:* 15 vs. 4 %, $p = 0.016$), and *TP53* and *ARID1A* were less frequently mutated *(TP53:* 25 vs. 58 %, $p < 0.001$; *ARID1A:* 14 vs. 28 %, $p = 0.050$). A prominently mutated gene in UCB, *Rb1*, was ubiquitously unaltered in the UTUC tumors analyzed (0 % in UTUC vs. 19% in UCB; $p < 0.001$). Unaltered *Rb1* has been shown to be a positive predictor of survival [36]. Differential *FGFR3* alteration frequencies trended toward significance (36 % in UTUC vs. 22 % in UCB, $p = 0.065$). In response, Mullane and Bellmunt profiled 19 UTUC samples finding variably concordant results [37]. While no alterations in *Rb1* were found in 59 high-grade UTUC tumors in the primary study, the smaller study found three *Rb1* alterations in 19 samples, supporting the need for independent validation. That being said, these data in total present evidence for biological similarities and differences between UTUC and UCB and may be practically relevant in considering certain therapeutic strategies.

Immunotherapy with checkpoint inhibitors, including both programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) antibodies, represents an exciting novel strategy to treat metastatic UC including UTUC. Several checkpoint inhibitors are in later-stage clinical development as first-line and second-line therapies for metastatic UC. Agents with trial results reported include pembrolizumab, avelumab, and atezolizumab. These agents, together with nivolumab and ipilimumab, are being evaluated in ongoing phase II and III trials (Table 2).

A phase Ib trial evaluated pembrolizumab, a PD-1 inhibitor, in recurrent, metastatic, or persistent UC whose tumors on immunohistochemistry showed ≥ 1 % PD-L1-positive cells in tumor nests or a PD-L1-positive band in stroma [38]. Among patients with measurable baseline disease, the objective response rate (ORR) was 25 %. At 12 months, 19% continued to maintain response. Notably, ORR was 38 % in PD-Ll-positive tumors. Avelumab is a PD-L1 inhibitor which demonstrated an ORR of 15.9 % in treatment-refractory metastatic UC in a phase Ib study. Durable responses were achieved in 13.6 % of patients [39]. Among tumors evaluable for PD-L1 expression, ORR was 40 % in PD-L1-positive tumors versus 9.1 % in PD-L1-negative tumors. Both pembrolizumab and avelumab have demonstrated promising outcomes and are being evaluated in phase III trials for second-line therapy in metastatic UC (NCT02256436 and NCT02603432, respectively).

Rosenberg and colleagues recently published outcomes from a phase II trial evaluating atezolizumab, a PD-L1 inhibitor [34]. The trial enrolled 316 patients who were either (1) chemotherapy-naïve and cisplatin-ineligible or (2) cisplatin-refractory. The trial incorporated the evaluation of immune cell (IC) PD-L1 expression (grading IC0–IC3), TCGA cluster subtype, and mutation load. UTUC was the primary site for 21 % of all patients and 16 % of patients who were IC2/3. The ORR for IC2/3, IC1/2/3 and all patients was 26, 18, and 15 %, respectively. Twelvemonth OS was 48 % in the IC2/3 group and 36 % in the intention-to-treat group compared to the historical rate of 20% in patients receiving second-line therapy [40]. Median OS for IC2/3, IC1/2/3 and all patients was 11.4, 8.8, and 7.9 months, respectively. Durable responses were achieved in patients with UTUC as well. With a

median follow-up of 11.7 months, 84 % of responders continued to maintain response. PD-L1 expression, cluster subtype, and mutation load were independently associated with drug response, and elevated PD-L1 expression on immune cells was associated with longer OS. Only 16 % of patients experienced grade 3/4 treatment-related adverse events; 5 % of patients experienced immune-mediated adverse events. Atezolizumab is an effective and well-tolerated treatment for second-line therapy in metastatic UC (including UTUC) and the FDA granted accelerated approval to atezolizumab on May 18, 2016, for the treatment of locally advanced or metastatic UC who have disease progression during or following platinum-based chemotherapy, or whose disease has worsened within 12 months of receiving platinum-based chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant). A phase III trial for atezolizumab compared to chemotherapy has completed enrollment (NCT02302807).

Post-chemotherapy lymphadenectomy and visceral metastasectomy

In 1994, a retrospective review demonstrated a pattern of recurrence that supported the aggressive removal of regional nodes [41]. Of patients with initial loco-regional UC treated with chemotherapy who relapse, 74 % present with recurrent disease in a similar location while the remainder present with visceral metastasis. In recent years, several detailed reports have emerged supporting the use of post-chemotherapy surgery as a consolidation strategy. The first report of post-chemotherapy lymphadenectomy (LND) in UTUC was limited by a small sample size [42]. In this report, 18 clinically node-positive patients underwent post-chemotherapy retroperitoneal lymph node dissection (RPLND) with concomitant radical nephroureterectomy. Because of the multicenter nature of the analysis, the study excluded a substantial number of patients due to inadequate RPLND. Despite this limitation, five-year cancer-specific survival was 44 %, comparing favorably to historical series of patients with clinically node-positive disease.

In a retrospective analysis, Necchi and colleagues evaluated the contribution of post-chemotherapy pelvic LND or RPLND on survival by reviewing 59 patients with advanced and metastatic UC, 28 of whom underwent postchemotherapy surgery, and demonstrated that in selected patients who achieve a clinical benefit from upfront chemotherapy, removal of residual disease is associated with a survival advantage [43]. On multivariate analysis, postchemotherapy surgery was associated with improved PFS and OS. Primary site was not prognostic. A Japanese multicenter analysis reported outcomes on 42 patients with UCB (50 %), UTUC (43 %), or both (7 %) who underwent metastasectomy for variable indications [44]. There were 15 RPLNDs, 5 distant LNDs, and 12 pulmonary resections with the remainder undergoing other surgeries. The aggregated 5-year OS was 31 %. On univariate analysis, primary tumor site was not prognostic, but metastasectomy for solitary node or lung metastasis was significantly associated with improved survival compared to other indications. Median OS was 81 vs. 19 months, respectively (29 months overall). As a comparison, the authors previously reported a median survival of 42 months for patients undergoing metastasectomy and 10 months for those who did not [45]. The authors reported no operative mortality. A report from the MD Anderson Cancer Center reviewed the outcomes of 55 patients with node-positive UCB who underwent postchemotherapy LND [46]. Median cancer-specific survival for all patients was 26 months. On multivariate

analysis, radiographic complete response (CR) and pathologic CR were significantly associated with improved survival. Notably, one-third of patients who achieved radiographic CR did not achieve pathologic CR. The 5-year cancer-specific survival was 66 % for patients with pathologically nodenegative disease vs. 12 % for those with pathologically node-positive disease ($p < 0.001$). Notably, the reported 90-day mortality rate was 1.8 %. While these series suggest some potential benefit to lymphadenectomy, the quality of the evidence suffers from potential selection bias and the retrospective nature of the studies.

While present studies have found no survival difference for post-chemotherapy LND in UTUC versus UCB [43, 44], certain factors appear to predict for improved outcomes in post-chemotherapy surgery. Patients with metastatic UC who respond well to chemotherapy may have improved survival. Siefker-Radtke and associates reported the 5-year survival for patients undergoing post-chemotherapy surgery is higher when patients experienced > 90 % response to chemotherapy (42 vs. 11 %) [47]. Interestingly, the 5-year survival for patients who achieved > 90 % response, including both those who did and did not undergo surgery, was also 42 %, challenging the role for surgery in patients who achieve a post-chemotherapy radiographic CR. That being said, other studies have demonstrated that the 5-year survival of node-positive patients undergoing post-chemotherapy surgery is higher with radiographic CR than with PR [46, 48]. Pathologic CR is also associated with improved survival [46]. The site of metastatic disease is also predictive. Metastasectomy for solitary lymph nodes or lung nodules is associated with a considerable improvement in survival compared to other indications (median OS: 81 vs. 19 months) [44]. Similarly, viable tumor in ≤ 2 lymph nodes at RPLND is associated with improved survival in UCB [49].

Insights into a potential role for visceral metastasectomy in UTUC may be extrapolated from studies involving UCB or both diseases. The first report on visceral metastasectomy followed 6 patients with metastatic UCB who underwent wedge resection of solitary pulmonary metastases. While patients with metastatic UC survive on average 13 months [7], the median survival in this cohort was 5 years [50]. In 2004, investigators from the MD Anderson Cancer Center reported on 31 patients who underwent metastasectomy of visceral or distant nodal metastasis. 33 % were alive after five years [51]. The most commonly resected site was the lung (77 %). Operative morbidity in patients who underwent lung resection included prolonged air leak in 12.5 % of patients, ileus in 8.3 %, and fever in 8.3 %. No operative mortality was reported.

Resection for either solitary lung or nodal metastasis is a positive prognostic factor [44]. One report of 18 patients undergoing pulmonary metastasectomy found that the 5-year survival rate after solitary metastasectomy was 86 versus 20 % for multiple metastasectomy with a 11 % postoperative infection rate overall [52]. The survival benefit seen in this study may result from its homogenous patient sample. Kim and colleagues reported outcomes of metastasectomy in patients with urinary tract cancer of any histology (63 % pure UC) [53]. The most commonly resected site was the lung (80 %) followed by lymph node (10 %). Pulmonary metastasectomy, compared to resection of other sites, was again a positive prognostic factor for time to progression (TTP) and OS (median TTP: 26 vs. 3 months; median OS: 43 vs. 13 months). At 3 years, 41 % were alive. Primary site was not prognostic ($p = 0.16$) nor were age, age-adjusted Charlson comorbidity score, and PS. A single

compared to multiple pulmonary metastasectomy was associated with longer TTP but not OS (TTP: 68 vs. 7 months, $p < 0.001$). The size of the lung metastasis was not correlated with improved outcomes. Conversely, another report of 32 patients undergoing pulmonary metastasectomy found that a pulmonary metastasis > 3 cm was a poor prognostic factor [54]. No operative mortalities were reported [53].

In total, these reports suggest that there may be a role for visceral metastasectomy in select patients. Pulmonary metastasectomy, especially for solitary disease, appears to confer the longest survival benefit. Nonetheless, these results must be cautiously interpreted due to their retrospective nature and small sample sizes. Additionally, each study had varying degrees of heterogeneity in primary site, administration and timing of chemotherapy, and resection sites; nevertheless, in view of the potential benefit, the results merit prospective validation.

To date, it is unclear whether UTUC compared to UCB differentially impacts survival following metastasectomy. Larger-sized cohorts are required to definitively answer this question. Any guidance with surgery in the metastatic setting involves extrapolation from studies including both UTUC and UCB. The current evidence suggests a potential benefit for post-chemotherapy lymphadenectomy and pulmonary metastasectomy, but further exploration using a larger and/or more homogenous patient cohort would provide valuable insight.

Conclusion

The management of metastatic UTUC requires a multidisciplinary approach involving medical oncologists, urologists, and radiation oncologists who often employ radiation therapy in the palliative setting. In the second-line metastatic setting, limited treatment options mandate the enrollment of patients onto clinical trials. Immunotherapy using checkpoint inhibitors has demonstrated great promise. In addition, the potential for novel targeted therapies has emerged from a new understanding of UC biology based on genomic profiling. There is also growing evidence that post-chemotherapy surgery may benefit select patients. In summary, the management of UTUC is extrapolated from studies of predominantly UCB and future studies must focus on multicenter collaborations to provide prospectively generated evidence to guide the management of metastatic UTUC.

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Table 1

Select clinical trials with reported outcomes

Phase	*n*	% UCB	% UTUC	Arm A	Arm B	Median survival (A vs. B; months)	*p* value	Notes	Reference
First-line therapy for cisplatin-eligible patients									
II	133	75	17	MVAC	-	13.3	-		[3]
III	269	87	NR	MVAC	Cisplatin	12.5 versus 8.2	0.002		[4]
III	263	85	13	DD-MVAC + G-CSF	MVAC	15.1 versus 14.9	–	5-year survival was significantly higher with DD-MVAC + G-CSF at 21.8 versus 13.5 % with MVAC.	[5,6]
III	405	100	0	GC	MVAC	13.8 versus 14.8	0.75		[7]
III	85	NR	NR	Paclitaxel + carboplatin	MVAC	13.8 versus 15.4	0.65		[8]
III	220	84	16	Docetaxel + cisplatin	DD-MVAC + G-CSF	9.3 versus 14.2	0.026	Survival difference was nonsignificant after adjusting for prognostic factors ($p = 0.089$).	[9]
III	130	83	13	Dose-dense GC + G-CSF	DD-MVAC + G-CSF	18.0 versus 19.0	0.98		[10]
III	626	82	13	PGC	GC	15.8 versus 12.7	0.075		[11]
II	63	83	18	Sunitinib + GC	-	12	-		[12]
II	98	70	30	Sorafenib + GC	Placebo + GC	11.3 versus 10.6	0.66		[13]
First-line therapy for cisplatin-ineligible patients									
II/III	238	74	22	Carbo/gem	M-CAVI	9.3 versus 8.1	0.64	Criteria: (1) GFR < 60 but > 30 ml/mi; and/or (2) PS of 2. Severe acute toxicity was 9.3 % in GC versus 21.2 % in M-CAVI.	[16]
II	51	61	39	Bevacizumab + carbo/gem	–	13.9	–	Criteria: (1) KPS 60–70 %; (2) CrCl < 60 ml/min; (3) visceral metastasis; and/or (4) solitary kidney.	[17]
I/II	32	100	0	Split-dose cisplatin (day 1 and 8) + gemcitabine (21-day cycle)	-	16	-	Criteria: (1) WHO PS 0–2 and (b) GFR > 40 ml/min.	[18]
-	38	97	0	Split-dose cisplatin (day 1 and 15) + gemcitabine (28-day cycle)	-	8.5	-	Criterion: CrCl between 35 and 59 ml/min.	[19]
II	69	52	46	Vinflunine + gemcitabine	Vinflunine + carboplatin	14.0 versus 12.8	0.86	Criteria: (1) ECOG PS 0 or 1 and (2) cisplatin-ineligible. defined as calculated CrCl < 60 but ≥ 30 mL/min and/or NYHA class II/III heart failure.	[20]
Second-line therapy									
III	370	NR	NR	Vinflunine + BSC	BSC	6.9 versus 4.6	0.287	Significant after adjusting for “eligible” patients.	[21]
II	47	NR	NR	Pemetrexed	-	9.6	-		[22]

Phase	*n*	% UCB	% UTUC	Arm A	Arm B	Median survival (A vs. B; months)	*p* value	Notes	Reference
II	31	94	6	Paclitaxel	-	7.2	-		[23]
II	30	83	17	Docetaxel	-	9	-		[24]
II	148	NR	NR	Ramucirumab + docetaxel	Docetaxel	10.4 versus 9.2	0.201	Median PFS: 5.4 months with arm A versus 2.8 months with arm B ($p = 0.0002$). Trial included a third arm, icru- cumab + docetaxel, which did not improve PFS.	[25]
Immunotherapy									
Ib	33	NR	NR	Pembrolizumab	-	NR	-	Criteria: (1) tumors on immuno- histochemistry showed ≥ 1 % PD-Ll-positive cells in tumor nests or a PD-Ll-positive band in stroma and (2) recurrent or persistent metastatic UC. ORR was 25 %. 12-month PFS was 19%.	[38]
Ib	44	NR	NR	Avelumab	-	NR	-	Studied as second-line therapy. ORR was 15.9 % overall and 40 % in PD-Ll-positive tumors.	[39]
II	316	74	21	Atezolizumab	-	7.9	-	Criteria: (1) cisplatin-ineligible and chemo-naive or (2) cisplatin- refractory. ORR for the IC2/3, IC1/2/3, and overall cohort were 26, 18, and 15 %, respectively. Median survival for the IC2/3, IC1/2/3, and overall cohorts were 11.4, 8.8, and 7.9 months, respectively.	[34]

BSC best supportive care, *Carbo/gem* carboplatin plus gemcitabine, *CrCl* creatinine clearance, *DD-MVAC* dose-dense methotrexate, vinblastine, doxorubicin, plus cisplatin, *G-CSF* granulocyte- colony stimulating factor, *GC* gemcitabine plus cisplatin, *GFR* glomerular filtration rate, *IC* immune cell PD-L1 expression grade, *KPS* Kamofsky performance status, *M-CAVI* methotrexate, carboplatin, plus vinblastine, *MVAC* methotrexate, vinblastine, doxorubicin, plus cisplatin, *NR* not reported, *NYHA* New York Heart Association, *ORR* objective response rate, *PGC* paclitaxel, gemcitabine plus cisplatin, *PFS* progression-free survival, *PS* performance status, *UC* urothelial carcinoma, *UCB* urothelial carcinoma of the bladder, *UTUC* upper tract urothelial carcinoma, *WHO* World Health Organization

Table 2

Planned, ongoing, and completed trials incorporating targeted or immune therapy

lst-line, CE	lst-line, CI	2nd-line	Phase	Closed	Novel target	Intervention arm(s)	Control arm (if applicable)	ClinicalTrials.gov identifier
Targeted therapies								
		X	II	X	EGFR, HER2	Afatinib		NCT02122172
		X	II		FGFR3	B-701 + docetaxel	Placebo + docetaxel	NCT02401542
		X	II		Cancer stem cell growth	BBI503		NCT02232646
X			III	X	VEGF	Bevacizumab + GC	Placebo + GC	NCT00942331
		X	II	X	FGFR3	BIBF1120		NCT02278978
		X	II	X	PI3 K	Buparlisib		NCT01551030
		X	II	X	c-Met, VEGFR-2, RET	Cabozantinib		NCT01688999
		X	II		c-Met, RON	Crizotinib		NCT02612194
	X		II	X	mTOR	Everolimus ± paclitaxel		NCT01215136
		X	II	X	mTOR	Everolimus		NCT00805129
		X	II		FGFR	JNJ-42756493		NCT02365597
X	X		II/III	X	HER2, HER1	Lapatinib after lst-line therapy	Placebo after 1st-line therapy	NCT00949455
		X	II	X	HDAC	Mocetinostat		NCT02236195
		X	II	X	Hsp27	OGX-427 + Docetaxel	Docetaxel	NCT01780545
		X	II		CDK4, CDK6	Palbociclib		NCT02334527
		X	III		VEGFR-2	Ramucirumab + docetaxel	Placebo + docetaxel	NCT02426125
		X	II	X	mTOR	Temsirolimus		NCT01827943
		X	II		FTase	Tipifarnib		NCT02535650
X			II		ATR kinase	VX-970 + GC	GC	NCT02567409
Immunotherapy								
		X	III	X	PD-L1	Atezolizumab	Vinflunine, paclitaxel, or docetaxel	NCT02302807
X	X		III		PD-L1	Avelumab + BSC after lst-line therapy	BSC after 1st-line therapy	NCT02603432
X			II	X	CTLA-4	Ipilimumab + GC		NCT01524991
		X	II		PD-1; CTLA-4	Nivolumab then nivolumab + ipili- mumab at progression		NCT02553642
		X	II	X	PD-1	Nivolumab		NCT02387996

lst-line, CE	lst-line, CI	2nd-line	Phase	Closed	Novel target	Intervention arm(s)	Control arm (if applicable)	ClinicalTrials.gov identifier
X	X		II		PD-1	Pembrolizumab after lst-line therapy	Placebo after 1st-line therapy	NCT02500121
	X		II		PD-1	Pembrolizumab		NCT02335424
		X	III	X	PD-1	Pembrolizumab	Vinflunine, paclitaxel, or docetaxel	NCT02256436
			II		PD-1	Pembrolizumab + paclitaxel		NCT02581982
		X	II	X	PD-1; Bruton tyrosine kinase	Pembrolizumab ± ACP-196		NCT02351739
		X	II		PD-1	Recombinant fusion protein sEphB4-HSA + pembrolizumab		NCT02717156

CLinicalTrials.gov was accessed on May 2, 2016, to compile a table of planned, ongoing, and completed trials (verified since May 2014, completed since May 2015, and had no published results per ClinicalTrials.gov) for metastatic UC, including UTUC

ATR ataxia telangiectasia and Rad3 related, *BSC* best supportive care, *CDK4* cyclin-dependent kinase 4, *CDK6* cyclin-dependent kinase 6, *CE* cisplatin-eligible, *CI* cisplatin-ineligible, *CTLA-4* cytotoxic T lymphocyte-associated protein 4, *EGFR* epidermal growth factor receptor, *FGFR* fibroblast growth factor receptor, *FGFR3* fibroblast growth factor receptor 3, *FTase* farnesyltransferase, *GC* gemcitabine plus cisplatin, *HDAC* histone deacetylase, *HER1* human epidermal growth factor receptor 1, *HER2* human epidermal growth factor receptor 2, *Hsp27* heat shock protein 27, *mTOR* mechanistic target of rapamycin, *PD-1* programmed death 1, *PD-L1* programmed death ligand 1, *PI3 K* phosphoinositide 3-kinase, *RET* rearranged during transfection, *RON* Recepteur d'Origine Nantais, *sEphB4-HSA* soluble ephrin type-B receptor 4-human serum albumin, *VEGF* vascular endothelial growth factor, *VEGFR-2* vascular endothelial growth factor receptor 2