TAU TRANSLATIONAL ANDROLOGY AND UROLOGY
A RISING JOURNAL FOR THE SCIENCE AND ART OF ANDROLOGY AND UROLOGY
IMPACT FACTOR 3.15

Peer Review File

Article information: https://dx.doi.org/10.21037/tau-21-47

Reviewer #1

General comments:

The review covers the important topic of medical treatment of UTUC, which is highly relevant.

Comment 1: There are some sentences with suboptimal clarity in regard to grammar and spelling errors (see below, but not limited to the below mentioned). Maybe the paper could be improved by the assistance of a native speaker.

The manuscript has been completely revised and checked for grammar and spelling errors (see track changes).

Comment 2: In general, it should be clearly stated which data is explicitly on UTUC vs. mixed trials with UTUC subgroups vs. bladder only trials, which are mentioned as analogy.

Presented data has been clarified and subgroups of patients with UTUC added when available.

Specific comments:

Abstract:

Comment 3: "cancer specific mortality in the majority of patients once the cancer recurs." Incomplete sentence, please revise.

Abstract has been completely revised.

Introduction:

Comment 4: "Beside proven risk factors such as smoking [4]and aristolochic acid [5], several environmental factors, and geneAc predisposing [6] implicated in UTUC carcinogenesis [7, 8]." Verb is missing, please revise.

Sentence has been deleted.

Comment 5: "Tumor grade can be accurately determined by small ureterorenoscopic biopsies in most of the cases, but tumor stage is unreliable" Available literature shows that grading is also very unreliable with upstaging in 30-40%. Please revise and cite the appropriate literature (e.g. Dev et al. 2017, Smith et al. 2011).

Sentence has been revised, clarified and additional literature used for cittation purposes.

"Pathologic evaluation of small ureterorenoscopic biopsies can be demanding. Tumor grade can be determined correctly in the majority of patients with high grade UTUC, with a concordance between endoscopic biopsy and nephroureterectomy specimen of up to >90% (6, 7); while upgrading of low grade biopsies occurs in a significant number of patients (7-9). Determination of tumor stage is accepted to be unreliable based on biopsy only (6, 8)."

Neoadjuvant immunotherapy:

Comment 6: "In the neoadjuvant seong, two single arm phase 2 trials with pembrolizumab (PURE-01) [37] and atezolizumab (ABACUS) [38] in paAents with non-metastaAc muscle invasive or locally advanced UBC have been published recently." These trials were designed for bladder cancer, not UTUC – this should be clarified (see above).

Presented data has been clarified and subgroups of patients with UTUC added when available.

Reviewer #2

MAJOR:

Comment 1: The entire manuscript including the abstract requires significant English language revision. There are countless errors including incomplete sentences, and the paper reads poorly.

The manuscript has been completely revised and checked for grammar and spelling errors (see track changes).

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Comment 2: Consider adding some tables to summarize specific topics (e.g. studies on neoadjuvant chemo) – and reduce the text in the corresponding sections.

Tables for ongoing clinical trials for UTUC in the neoadjuvant and adjuvant setting have been added to the manuscript. (Table 1 and 2)

Comment 3: The authors cite many trials in mixed upper tract and lower tract urothelial carcinoma but only rarely acknowledge the subgroup analyses of UTUC vs bladder ca. Please revise where ever possible – especially with all the recent larger phase 3 trials testing IO, erdafitinib and EV (e.g. adjuvant IO; first line and second line IO; switch maintenance IO; maybe also first line chemo?).

Presented data has been clarified and subgroups of patients with UTUC added when available.

OTHER:

Comment 3: The Introduction is rambling and does not state an objective for the manuscript. Keep the Intro focused on systemic therapy, which is the topic of the chapter (especially if there are also other papers in this topic issue on UTUC). The paragraph on cisplatin eligibility does not fit as written.

The introduction has been revised and the paragraph cis-eligibility has bene deleted.

Comment 4: Even a narrative review can have a more specific description of how the review was conducted in the Methods section.

The method section has been completely revised.

Comment 5: The authors state that ongoing phase III RCTs are struggling with poor accrual – on what is this statement based?

The statement has been rephrased and clarified.
"Randomized phase 3 trials are ongoing, though patient recruitment can be challenging, in part, because of the rarity of the disease (22-24)."

Comment 6: What proportion of patients become ineligible for cisplatin after nephroureterectomy? Be specific " –substantial" is too vague. This is a critical point.

"Though, the rational to use NAC for treatment of non-metastatic high-risk UTUC might be even greater than that in MIBC, as only half of patients undergoing RNU are eligible for a cisplatin-based chemotherapy before surgery and only one out of five patients remains eligible after RNU (26), mostly due to deterioration of renal function (27)."

Comment 7: The discussion of neoadjuvant chemotherapy is chaotic and bounces around. Please organize this logically. Consider replacing a lot of the text with a table. Please include the numbers of patients who have ypT1 or less disease in the various studies– this is a high proportion.

This paragraph has been completely revised and pCR and pathological downstaging added to the discussion.

"Recent systematic reviews and meta-analyses found a pCR rate (ypT0N0M0) of 11% (95% CI 8-15%), a pathologic partial response rate (pPR; ≤ypT1N0M0) of 43% (95% CI 34-52%) and a pathological downstaging (cT>pT) in 33% (95%CI 14-52%) of cases (30). NAC was associated with higher rates of pathological downstaging (RR 6.48, 95% CI 2.05-20.44, $p = 0.001$) and pCR (RR 18.46, 95% CI 3.34-99.24, $p = 0.001$) (31). Pathological downstaging was found to be the strongest prognostic factor for recurrence-free survival (RFS; HR 0.2, $p <0.001$), cancer specific survival (CSS; HR 0.19, $p <0.001$) and overall survival (OS; HR 0.40, $p <0.001$) in an international observational study in patients undergoing NAC and RNU for high risk UTUC (32)."

Comment 8: If describing URANUS, please indicate trial design briefly – is this NAC vs adjuvant chemo?

"Several ongoing clinical trials are currently evaluating NAC in UTUC (Table 1) including the multi-centric URANUS trial, which aims to explore the feasibility of perioperative chemotherapy in UTUC at various European centers (NCT02969083). Patients who are eligible for a cisplatin-based chemotherapy are randomized to

receive either cisplatin-based NAC or AC. Patients ineligible for cisplatin-based perioperative chemotherapy undergo RNU only."

Comment 9: The section on neoadjuvant IO describes the study results in MIBC in detail – the authors need to re-focus this section on what is going on in UTUC. Keep the MIBC part brief. Discussion of PD-L1 staining between TURBT and RC is irrelevant to current paper.

Section has been completely revised. And a table with ongoing neoadjuvant clinical trials added to the masnucript. (Table 1).

In the neoadjuvant setting of UBC, two single-arm, phase 2 trials with pembrolizumab (PURE-01) (34) and atezolizumab (ABACUS) (35) in patients with non-metastatic or locally advanced UBC have been published recently. These trials included unselected patients and used a comparatively low number of treatment cycles in order to not delay potentially curative surgery (34-37). Though, no patients with UTUC were included into these trials.
At time of radical cystectomy (RC), neoadjuvant CPI treatment resulted in a pCR rate of 31% and 42% for atezolizumab and pembrolizumab, respectively. Response rates were dependent on tumor PD-L1 expression and increased in patients with PD-L1 positive tumors compared to those with PD-L1 negative tumors (37% vs. 25% for ABACUS (35) and 54% vs. 13% for PURE-01 (34)). Whether these improved pCR rates to neoadjuvant CPI according to PD-L1 status translate into a survival benefit, has to be determined. The adverse events were similar to those observed in clinical trials evaluating CPI in metastatic UC and no delay, nor failure to undergo RC was noted in both trials (34, 35).

With PURE-02, a multi-center prospective phase 2, single-arm trial is ongoing to evaluate pembrolizumab in the neoadjuvant setting in UTUC (38). This trial could have the potential to increase the generally low acceptance of neoadjuvant therapy in cancers of the upper and lower urothelial tract (39). In addition, several ongoing clinical trials evaluate the neoadjuvant treatment with novel targeting agents as monotherapy or in combination with chemotherapy (Table 1).

Comment 10: The authors should touch on the idea that MMR-deficient UTUC may

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be particularly susceptible to neoadjuvant IO.

Add a discussion about relative benefit of carbo vs cisplatin in POUT. This has big implications for practice.

Both comments have been implemented to the revised manuscript within the discussion and conclusion.

Comment 11: Please update the discussion of adjuvant IO to include results for CM2784 presented at GU ASCO – and include the subgroup analyses of patients with UTUC – discuss implications of these results – and possible explanations for lack of response in UTUC.

Updated results have been added and UTUC subgroups for clinical trials reported when available.

Comment 12: Please discuss potential for peri-operative FGFR inhibition – and mention ongoing trials like PROOF.

Ongoing trials with FGFR inhibition in neoadjuvant and adjuvant setting have been implemented in Table 1 and 2.

Comment 13: For discussion of systemic chemo for mUC the authors need to try harder to focus this on UTUC – it is not adequate simply to list results for trials that accrued predominantly bladder cancer patients.

Section and metastatic UC/UTUC has been revised completely..

Comment 14: List of FGFR alterations required for erdafitinib is incorrect.

According to BLC2001 trial FGFR3 mutation or FGFR2/3 fusion.

Comment 15: The statement based on reference 66 is very important – but it is not linked logically to the rest of the text.

"Genetic characterization revealed that UTUC is often associated with luminal-papillary characteristics and harbors high FGFR3, which correlates with a T-cell

depleted immune microenvironment (61) and therefore offers the potential as target for novel therapies."

Has been implemented at the beginning of the section on novel targeted therapies.

Comment 16: Update EV results to include recently published EV-301, and include comment on UTUC subgroup

"These results have been recently confirmed in the phase 3 trial of EV for the treatment of patients with locally advanced or metastatic urothelial carcinoma who had previously received platinum-containing chemotherapy and had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor (EV-301). Progression-free (5.55 vs. 3.71 months; HR (95% CI), 0.62 (0.51 to 0.75; P<0.001) and overall survival (12.88 vs. 8.97 months; HR (95%CI) 0.70 (0.56 to 0.89); P=0.001) were longer in the EV group than in the chemotherapy group. The clinical trial included 205 patients with UTUC (34%). Subgroup analysis based on location of the primary tumor revealed a significant benefit in terms of OS in patients with UBC (HR 0.67 (0.51–0.88)), while in patients with UTUC it did not reach statistical significance (HR 0.85 (0.57–1.27)) (66)."