Original Article

Clinical outcomes of immune checkpoint inhibitor plus nab-paclitaxel in metastatic upper tract urothelial carcinoma

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Background: Metastatic upper tract urothelial carcinoma (mUTUC) is a malignant cancer associated with poor prognosis. Few studies have investigated the clinical outcome of a recently developed combination regimen of programmed cell death 1 (PD-1) inhibitor plus nab-paclitaxel in mUTUC.

Methods: We retrospectively retrieved data from the electronic medical records of cisplatin-ineligible or cisplatin-refractory mUTUC patients from five participating Chinese centers, who received treatment of PD-1 inhibitor plus nab-paclitaxel between April 2018 and January 2022. Clinical response was assessed according to Response Evaluation Criteria in Solid Tumors criteria version 1.1 (RECIST 1.1). Duration of response (DOR), overall survival (OS), and progression-free survival (PFS) were evaluated by the Kaplan-Meier method.

Results: The confirmed overall response rate (ORR) was 14/34 (41.2%), and the disease control rate (DCR) was 24/34 (70.6%). Complete response (CR) was achieved in one case, partial response (PR) in 13 cases (38.2%), stable disease (SD) in 10 cases (29.4%), and progressive disease (PD) occurred in 10 cases (29.4%). After a median follow-up period of 16.0 months [95% confidence interval (CI): 9.9–22.1], 14 deaths were reported, with a median OS of 15.0 months (95% CI: 9.9–20.1); 22 progressions were reported, with a median PFS of 6.0 months (95% CI: 2.4–9.6). Patients with visceral metastasis had a similar PFS [hazard ratio (HR): 1.28, 95% CI: 0.53–3.09, P=0.574) and OS (HR: 1.94, 95% CI: 0.64–5.83, P=0.279] to patients with lymph node metastasis only.

Conclusions: This real-world study suggests that PD-1 inhibitor plus nab-paclitaxel is effective in cisplatin-ineligible and cisplatin-refractory mUTUC patients with acceptable toxicity, especially for patients with visceral metastasis.

Keywords: Immune checkpoint inhibitors; 130-nm albumin-bound paclitaxel; retrospective study; metastatic upper tract urothelial carcinoma (mUTUC); cisplatin-ineligible

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Introduction

Upper tract urothelial carcinoma (UTUC) is a malignant disease of the urinary system (1). It is less common than bladder cancer and constitutes of less than 10% of all urothelial tumors in western countries (1). However, it has a higher prevalence in China, with a rate of 9–30%. Moreover, over 9% of UTUC patients present with metastasis at diagnosis and with poor prognosis (2-4).

The management of metastatic UTUC (mUTUC) is mostly based on extrapolations from evidence derived from studies of metastatic urothelial carcinoma (UC) of the bladder (5,6). However, UTUC has distinct biological and clinical features from those of bladder cancer (7-9). UTUC occurs in the upper part of the urinary tract, which includes the renal pelvis and the ureter, leading to impaired renal function and inherent frailty more frequently. Generally, UTUC is often diagnosed at a more advanced stage than bladder carcinoma and associated with poor prognosis. The genomic profiles of UTUC and bladder cancer exhibit distinctions as well. For instance, fibroblast growth factor receptor 3 (*FGFR3*), along with telomerase reverse transcriptase (*TERT*) promoter, lysine methyltransferase 2D (*KMT2D*), cyclin dependent kinase in*hi*bitor 2A (*CDKN2A*), and tumor protein p53 (*TP53*), have been identified as frequently mutated genes in UTUC (10). And *FGFR3* mutations are more prevalent in UTUC when compared to lower urinary tract diseases (11). Because the treatment strategies for metastatic UC are evolving rapidly, more specific investigations for UTUC are urgently needed.

Platinum-based chemotherapy is the standard first-line treatment for all eligible UTUC patients, and is associated with a median overall survival (OS) time of 12–14 months (12). Specifically, the standard regimen of cisplatin plus gemcitabine showed a median OS of 13.8 months and an overall response rate (ORR) of 49% with relatively low toxicity, making it the primary treatment strategy when eligible (13,14). However, many UTUC patients are unable to receive cisplatin due to impaired renal function and inherent frailty resulting from the tumor burden. While carboplatin plus gemcitabine can serve as an alternative, its efficacy is often unsatisfactory (15). There is an urgent need for more effective treatments for this patient population.

In recent years, combining immunotherapy with anti-programmed cell death 1 (PD-1) checkpoint inhibitor has shown promising therapeutic effects. Investigations of the role of immunotherapy in treating metastatic UC have suggested that it should be the preferred treatment option for patients who are ineligible for cisplatin or who have not responded to cisplatin-based treatment (16-21). However, clinical differences may lead to different treatment responses in UTUC and bladder cancer, as UTUC only constituted a minor proportion of these studies. Previously, we reported comparable oncological outcomes between PD-1 inhibitor monotherapy and carboplatin plus gemcitabine in first-line treatment of cisplatin-ineligible UTUC patients (22). Meanwhile, PD-1 inhibitor monotherapy is associated with lower toxicity (22). The efficacy of PD-1 inhibitor monotherapy might correlate with various biomarkers, including PD-L1 expression (23). The combination of immunotherapy and other agents has also developed rapidly with promising effects (24). Maintenance immunotherapy has also been the standard care for disease stabilization after first-line cisplatin-based chemotherapy (25). Some targeted small molecule inhibitors, especially fibroblast growth factor receptor inhibitors, have shown promising effects on treating UC, but further investigations are still required based on the molecular characteristics of UTUC (26,27).

Nab-paclitaxel is a 130-nm albumin-bound paclitaxel,

Highlight box

Key findings

- Nab-paclitaxel improves the effect of PD-1 inhibitor in visceral metastasis.

What is known and what is new?

- Due to the low morbidity, research on the clinical outcomes of a recently developed combination regimen of PD-1 inhibitor plus nab-paclitaxel in metastatic UTUC is lacking.
- This real-world study suggests that PD-1 inhibitor plus nab-paclitaxel is active in cisplatin-ineligible and cisplatin-refractory metastatic UTUC patients with acceptable toxicity.

What is the implication, and what should change now?

- PD-1 inhibitor plus nab-paclitaxel could be used in the treatment of metastatic UTUC with acceptable toxicity, especially for patients with visceral metastasis.

which was found to be well-tolerated with an encouraging median progression-free survival (PFS) time of 6 months and an ORR of 27.7% in a second-line setting of metastatic UC (28). PD-1 inhibitor plus nab-paclitaxel may have enhanced clinical benefits in cisplatin-ineligible and cisplatin-refractory mUTUC patients. PEANUT and ABLE are the only two published studies that have investigated on the outcomes of PD-1 inhibitor pembrolizumab plus nab-paclitaxel in metastatic UC patients (29,30). Thus, high-level evidence associated with this combination therapy is still lacking and more investigations are warranted, especially in the real-world UTUC population.

Here, we present a multi-center retrospective study that aimed to evaluate the efficacy and safety profile of PD-1 inhibitor plus nab-paclitaxel combination therapy in cisplatin-ineligible and cisplatin-refractory mUTUC patients in China. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-404/rc).

Methods

Patient enrollment

Data were retrieved from the electronic medical records of 34 cisplatin-ineligible or cisplatin-refractory mUTUC patients who visited five participating centers in China and received treatment with PD-1 inhibitor plus nab-paclitaxel therapy between April 2018 and January 2022. The eligibility criteria were as follows: histologically-confirmed, cisplatin-ineligible or cisplatin-refractory mUTUC patients; treated with PD-1 inhibitor plus nab-paclitaxel therapy; aged ≥18 years; having undergone at least 1 radiological assessment [computed tomography (CT) and/or magnetic resonance imaging (MRI)]; available to evaluate the tumor response at least 2 months after the initiation of the combination therapy; and measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria (31). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Committee for Ethics of Ren Ji Hospital (No. KY2021-102). All participating hospitals/institutions were informed and agreed to the study. The requirement for individual consent for this retrospective analysis was waived.

Treatment and procedures

All patients were treated with the combination therapy of PD-1 inhibitor plus nab-paclitaxel. The PD-1 inhibitors included pembrolizumab (n=5, 14.7%), toripalimab (n=5, 14.7%), and tislelizumab (n=24, 70.6%). The anti-PD-1 antibody agent was administrated intravenously once every 3 weeks (day 1), with pembrolizumab at a dosage of 200 mg, toripalimab 3 mg/kg, and tislelizumab 200 mg. Nab-paclitaxel was administrated intravenously twice every 3 weeks (days 1 and 8) at a dosage of 125 mg/m^2. This dosage could be reduced in case of the need to manage adverse events (AEs). Treatment was continued until disease progression, intolerable toxicity, death, or the withdrawal of participation.

Assessments

Radiological assessments were performed by baseline CT and/or MRI of the abdomen, chest, and brain, as well as with bone scintigraphy; assessments were repeated every 2–3 months to evaluate tumor response according to RECIST 1.1 criteria. All AEs during the follow-up were evaluated according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (32).

Statistical analysis

Statistical analyses were performed using the software SPSS 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). PFS was defined as the duration from the initiation of combination therapy to disease progression or death. OS was defined as the duration from the initiation of combination therapy to death from any cause. The duration of response (DOR) was defined as the duration from the initiation of combination therapy in patients with a complete response (CR) or partial response (PR) to progressive disease (PD) or death. PFS, OS, and DOR curves were evaluated by Kaplan-Meier analysis, and compared among groups by the log-rank test. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 34 mUTUC patients who received the combination therapy of PD-1 inhibitor plus nab-paclitaxel were included in this study. Figure S1 shows the flow chart of patient enrollment and exclusion. The main baseline characteristics of the entire cohort are shown in *Table 1*.

Table 1 Baseline characteristics of the 34 metastatic UTUC patients who received combination therapy of PD-1 inhibitor plus nab-paclitaxel

Characteristics	N (%) or median (range)
Patient No.	34
Age, years	62.5 (38.0–82.0)
Gender	
Male	22 (64.7)
Female	12 (35.3)
Baseline ECOG	
0–1	21 (61.8)
≥2	13 (38.2)
Tumor site	
Renal pelvis	15 (44.1)
Upper urothelial tract	19 (55.9)
Post-nephroureterectomy	
Yes	25 (73.5)
No	9 (26.5)
Laterality	
Left	17 (50.0)
Right	17 (50.0)
Histology	
Pure urothelial	31 (91.2)
Mixed urothelial	3 (8.8)
Prior treatment	
Yes	
Cisplatin refractory	18 (52.9)
No	
Cisplatin ineligible	16 (47.1)
Renal function	
Normal	21 (61.8)
Impaired	13 (38.2)
Duration of treatment, months	6.5 (2.0–15.0)
Metastasis	
Visceral	25 (73.5)
Liver	14 (41.2)
Lung	13 (38.2)
Bone	11 (32.4)
Lymph nodes only	9 (26.5)
Bajorin risk groups	
0	7 (20.6)
1	16 (47.1)
2	11 (32.4)

UTUC, upper tract urothelial carcinoma; PD-1, programmed cell death 1; ECOG, Eastern Cooperative Oncology Group.

Table 2 Treatment response in combination therapy

Response	N (%)
Objective response	14 (41.2)
Disease control	24 (70.6)
Best response	
Complete response	1 (2.9)
Partial response	13 (38.2)
Stable disease	10 (29.4)
Progressive disease	10 (29.4)

In brief, 64.7% of patients were male, and the median age was 62.5 years (range, 38.0–82.0 years). Thirteen (38.2%) patients had a baseline Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥2, and 18 (52.9%) patients had failed first-line cisplatin plus gemcitabine. Twenty-five (73.5%) patients had previously undergone nephroureterectomy and experienced recurrence with metastasis, 9 patients (26.5%) were diagnosed with metastasis without undergoing nephroureterectomy. A total of 13 (38.2%) patients had impaired renal function, 25 (73.5%) presented with visceral metastasis, and 9 (26.5%) presented with lymph node metastasis only. The median duration of treatment was 6.5 months (range, 2.0–15.0 months).

Treatment response

The best tumor responses for the 34 patients evaluated according to RECIST 1.1 are shown in *Table 2*. The confirmed ORR was 14/34 (41.2%) and the disease control rate (DCR) was 24/34 (70.6%). Only 1 (2.9%) patient achieved CR, 13 (38.2%) achieved PR, 10 (29.4%) had stable disease (SD), and 10 (29.4%) had PD. Figure S2 demonstrates a significant reduction of lung metastasis for a patient after undergoing a 2-month treatment of

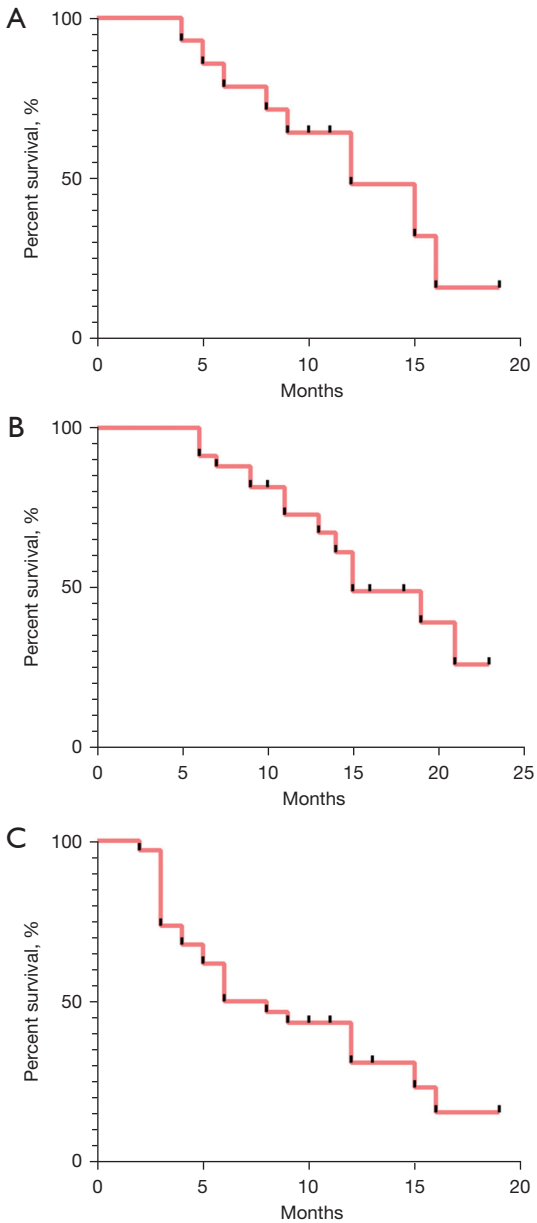

Figure 1 DOR (A), OS (B), and PFS (C) of metastatic UTUC patients treated with combination therapy. DOR, duration of response; OS, overall survival; PFS, progression-free survival; UTUC, upper tract urothelial carcinoma

tislelizumab plus nab-paclitaxel.

Survival outcomes

After a median follow-up period of 16.0 months [95% confidence interval (CI): 9.9–22.1], the median DOR was 12.0 months (95% CI: 5.8–18.2) (*Figure 1A*). There were two endpoints reached: 14 deaths were reported, with a median OS time of 15.0 months (95% CI: 9.9–20.1) (*Figure 1B*); 22 progressions were reported, with a median PFS time of 6.0 months (95% CI: 2.4–9.6) (*Figure 1C*). Patients with visceral metastasis showed a similar PFS time [hazard ratio (HR): 1.28, 95% CI: 0.53–3.09, P=0.574, *Figure 2A*] and OS time (HR: 1.94, 95% CI: 0.64–5.83, P=0.279, *Figure 2B*) to those with lymph node metastasis only.

Safety

AEs led to the discontinuation of nab-paclitaxel in 4 (11.8%) patients, and the discontinuation of both nab-paclitaxel and PD-1 inhibitor in 1 (2.9%) patient (*Table 3*). Specific AEs observed during the treatment period are listed in *Table 4*. Any-grade AEs were observed in 27 (79.4%) patients. The most common AEs included alopecia (52.9%), peripheral neuropathy (41.2%), fatigue (29.4%), anemia (23.5%), and neutropenia (23.5%). Grade 3–4 AEs were seen in 11 patients (32.4%), and the most common included anemia (8.8%), neutropenia (8.8%), and peripheral neuropathy (5.9%).

Discussion

Cisplatin-based chemotherapy has previously shown clinical benefits and good tolerability as the standard first-line treatment for metastatic UC (12). However, up to 50% of patients are considered cisplatin-ineligible because of impaired renal function or with poor performance status (33); the criteria for cisplatin ineligibility include at least one of the following: performance status >1, glomerular filtration rate ≤60 mL/min, audiometric hearing loss grade ≥2, peripheral neuropathy grade ≥2, or New York Heart Association (NYHA) class III/IV heart failure (33). Considering the rapid development of immunotherapy and the observed encouraging level of clinical efficacy and good safety profile of nab-paclitaxel in the second-line management of metastatic UC (28), the regimen of PD-1 inhibitor plus nab-paclitaxel could be considered as an alternative treatment choice for cisplatin-ineligible and cisplatin-refractory mUTUC patients.

Carboplatin plus gemcitabine was previously recommended by the European Organization for Research and Treatment of Cancer as one of the standard forms of care for first-line cisplatin-ineligible patients; the reported ORR was 36.1%, but this efficacy was inferior to cisplatin

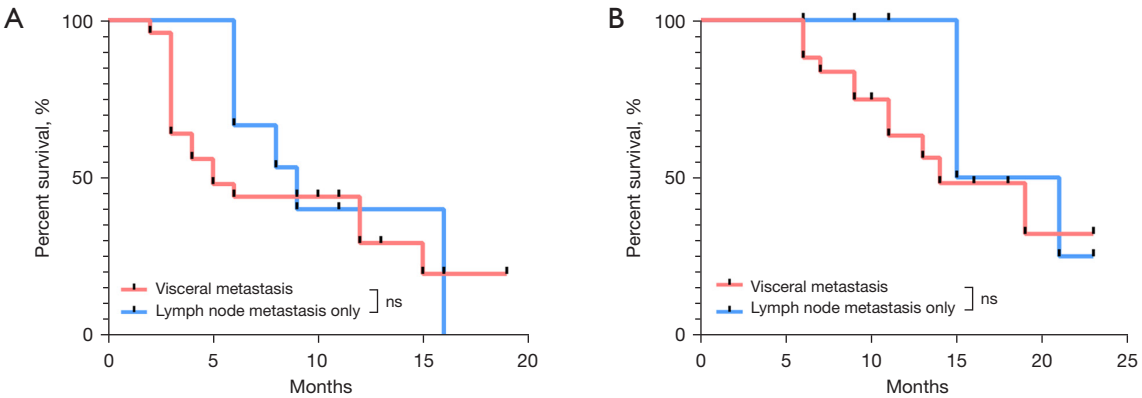

Figure 2 PFS (A) and OS (B) times of metastatic UTUC patients treated with combination therapy. PFS, progression-free survival; ns, not significant; OS, overall survival; UTUC, upper tract urothelial carcinoma.

Table 3 Safety summary

AEs	Any grades, n (%)	Grade 3–4, n (%)
All caused AEs	27 (79.4)	11 (32.4)
Nab-paclitaxel-related AEs	24 (70.6)	10 (29.4)
PD-1 inhibitor-related AEs	13 (38.2)	3 (8.8)
Treatment discontinuation due to AEs		
Nab-paclitaxel	4 (11.8)	3 (8.8)
PD-1 inhibitor	–	–
Both	1 (2.9)	1 (2.9)

AEs, adverse events; PD-1, programmed cell death 1.

plus gemcitabine (ORR of 49%) (13,34). Other single-agent chemotherapy and non-platinum combination treatments such as gemcitabine plus paclitaxel and gemcitabine plus vinflunine have also been shown to be inferior to carboplatin-based regimens (35-38).

In recent years, several studies have investigated the efficacy of anti-PD-1 immunotherapy since it gained the US Food and Drug Administration approval (16-19,39). In the phase II KEYNOTE-052 study, pembrolizumab achieved an ORR of 22% in a subset of 19% of enrolled cisplatin-ineligible UTUC patients (18). In another UTUC subset of the phase II IMvigor210 study, which occupied 28% of the entire UC cohort, atezolizumab was associated with an ORR of 39% (19). The KEYNOTE-361, IMvigor130, and DANUBE studies reported ORRs ranging from 23% to 30% for anti-PD-1 monotherapy in first-line metastatic UC in which UTUC patients comprised of 18–25% of those enrolled (16,17,39). However, these three studies did not include specific data for the UTUC subset.

Given the unsatisfactory efficacy of carboplatin and PD-1 inhibitor monotherapy, it becomes imperative to explore a combination strategy involving PD-1 inhibitors and chemotherapy to achieve a synergistic effect. For example, IMvigor130 showed a PFS benefit for atezolizumab plus platinum-based chemotherapy compared with chemotherapy alone, but the cisplatin-ineligible subpopulation was not analyzed.

According to Chinese Society of Clinical Oncology (CSCO) guideline, nab-paclitaxel, docetaxel and paclitaxel belong to the same class of paclitaxel drugs, which can be used as chemotherapy drugs for advanced UTUC. The combination of immunotherapy and chemotherapy is also available in the treatment of UTUC. The ABLE and PEANUT studies reported ORRs of 56.3% and 44.4% in cisplatin-ineligible or platinum-refractory metastatic UC patients who received pembrolizumab plus nab-paclitaxel, respectively (29,30). Two recent clinical trials also demonstrated the efficacy of immune checkpoint inhibitor plus nab-paclitaxel in UC (40,41). To evaluate this combination regiment in real-world setting, we conducted the first retrospective, multi-center, real-world study to evaluate the clinical efficacy and safety profile of this combination therapy in specific mUTUC patients. Our findings revealed an ORR of 41.2% among first-line cisplatin-ineligible and second-line cisplatin-refractory mUTUC patients. Notably, the combination therapy showcased a median PFS of 6.0 months and an OS of 15.0 months, with a median DOR reaching 12.0 months. These results, coupled with insights from prior research, highlight that the PD-1 inhibitor and nab-paclitaxel

Table 4 Adverse events observed during combination therapy

Adverse events	Any grades, n (%)	Grade 3–4, n (%)
Alopecia	18 (52.9)	0
Peripheral neuropathy	14 (41.2)	2 (5.9)
Fatigue	10 (29.4)	0
Anemia	8 (23.5)	3 (8.8)
Neutropenia	8 (23.5)	3 (8.8)
Thrombocytopenia	4 (11.8)	1 (2.9)
Rash	4 (11.8)	1 (2.9)
Pruritus	4 (11.8)	0
Arthralgia	3 (8.8)	1 (2.9)
ALT increase	3 (8.8)	1 (2.9)
AST increase	3 (8.8)	1 (2.9)
Diarrhea	3 (8.8)	0
Constipation	2 (5.9)	0
Dysgeusia	2 (5.9)	0
Fever	2 (5.9)	0
Anorexia	2 (5.9)	0
Nausea	2 (5.9)	0
Pneumonia	2 (5.9)	0
Hypothyroidism	2 (5.9)	0
Nall toxicity	1 (2.9)	0
Infections	1 (2.9)	0
Vomiting	1 (2.9)	0
Muscle weakness	1 (2.9)	0
Disturbance of consciousness	1 (2.9)	0
Dizziness	1 (2.9)	0
Paresthesia	1 (2.9)	0

ALT, alanine transaminase; AST, aspartate transaminase.

regimen delivers more substantial advantages for cisplatin-ineligible and cisplatin-refractory patients, surpassing the benefits of carboplatin plus gemcitabine or PD-1 inhibitor monotherapy, leading to an amplified ORR. Moving forward, studies with larger sample sizes and evaluation of specific subgroups are imperative. Moreover, the realm of combination regimens is poised to expand, offering enhanced avenues for optimizing clinical patient management.

In the previous first-line treatment of cisplatin-ineligible metastatic UC, carboplatin plus gemcitabine was associated with a median OS time of 9.3 months (34), whereas PD-1 inhibitors were associated with a median OS of 13.2–15.9 months, and a generally short PFS of 2.3–2.7 months (16-19,39). Survival data for the UTUC subset were limited in previous studies, with the only available results of an OS of 7.9 months from the IMivigor210 study and 10.9 months from IMivigor211 (42). Our study observed a median PFS of 6.0 months and a median OS of 15.0 months for PD-1 inhibitor plus nab-paclitaxel therapy, which was numerically superior to that of PD-1 inhibitor monotherapy in the UTUC subset.

PD-1 inhibitor monotherapy is typically considered less responsive for patients with visceral metastasis (16-19,39). In our study, combination therapy achieved a similar PFS (HR: 1.28, 95% CI: 0.53–3.09, P=0.574) and OS (HR: 1.94, 95% CI: 0.64–5.83, P=0.279) among patients with visceral metastasis and those with lymph node metastasis only. This indicates that the addition of nab-paclitaxel may improve the effect of PD-1 inhibitors in visceral metastasis.

The safety profile is an important issue which can restrict the use of combination therapy. In our study, 27 (79.4%) patients had at least one AE, with the most common being alopecia (in 52.9% of patients). In combination therapy, most AEs are attributed to nab-paclitaxel, with the addition of PD-1 inhibitor not having been previously reported to increase toxicity compared with nab-paclitaxel alone (28). Herein, the most common grade 3–4 AEs were observed in 11 (32.4%) patients, including 8.8% of anemia, 8.8% of neutropenia, and 5.9% of peripheral neuropathy, which was similar to the findings reported for nab-paclitaxel monotherapy (28). Encouragingly, only four (11.8%) patients discontinued nab-paclitaxel, and only one (2.9%) discontinued both nab-paclitaxel and PD-1 inhibitor because of AEs. Moreover, the rates of grade 3–4 AEs and drug discontinuation resulting from toxicity in our study were both much lower than those of platinum plus gemcitabine and the combination of PD-1 inhibitor and platinum plus gemcitabine (16).

Our study has the following limitations. The small sample size restricted the accurate interpretation of survival outcomes like DOR, OS and PFS. Low detection rate of PD-L1 expression on pathology prevented the assessment of combination therapy efficacy in subgroups of high and low PD-L1 expression. Toripalimab and tislelizumab, which were only available in China, were the most often included PD-1 inhibitors in our study; this reduced the broad applicability of our results. The retrospective design

introduced potential population collection bias and may lead to underestimated AEs. Nevertheless, our study yielded important evidence from a cohort of real-world patients from five high-volume medical centers.

Conclusions

PD-1 inhibitor plus nab-paclitaxel therapy is effective in cisplatin-ineligible and cisplatin-refractory mUTUC patients, and is associated with acceptable levels of toxicity, especially in patients with visceral metastasis.

Clinical practice points

UTUC accounts for approximately 5–10% of all UC cases worldwide and 20–30% of UC cases in China. As a result of the low morbidity, it is challenging to conduct substantial clinical trials specific for UTUC, and high-level evidence is lacking. mUTUC is commonly characterized by impaired renal function and inherent frailty, in which the administration of first-line platinum-based chemotherapy is challenging. Here, we aimed to retrospectively explore the efficacy and safety of a recently developed combination regimen of PD-1 inhibitor plus nab-paclitaxel in an mUTUC population. Our multi-center real-world study suggested that PD-1 inhibitor plus nab-paclitaxel is effective in cisplatin-ineligible and cisplatin-refractory mUTUC patients with acceptable toxicity, especially for patients with visceral metastasis. We presume that our work may contribute significantly to the management of PD-1 inhibitor plus nab-paclitaxel as a first-line or second-line treatment for cisplatin-ineligible or cisplatin-refractory mUTUC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-404/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Committee for Ethics of Ren Ji Hospital (No. KY2021-102). All participating hospitals/institutions were informed and agreed to the study. The requirement for individual consent for this retrospective analysis was waived.

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