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The efficacy and safety of first-line treatment in cisplatin-ineligible advanced upper tract urothelial carcinoma patients: a comparison of PD-1 inhibitor and carboplatin plus gemcitabine chemotherapy

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ABSTRACT

Although several programmed cell death (PD)-1 inhibitors are approved for the first-line treatment of advanced urothelial carcinoma, their efficacy remains unknown in cisplatin-ineligible patients with upper tract urothelial carcinoma (UTUC) compared with gemcitabine plus carboplatin. Data for patients with UTUC were retrospectively retrieved from the electronic medical records of nine institutions between 2018 and 2021. Patients considered ineligible for cisplatin who received either PD-1 inhibitors (n = 70) or gemcitabine plus carboplatin (n = 53) were included. Efficacy was assessed using Response Evaluation Criteria in Solid Tumors. Median progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The objective response rate (ORR) was comparable between the PD-1 inhibitor and carboplatin–gemcitabine groups (38.6% versus 41.5%). Median PFS was 5.0 months (95% confidence interval [CI]: 2.0–8.0) in the PD-1 inhibitor group, versus 7.0 months (95% CI: 5.8–8.2) in the carboplatin–gemcitabine group (hazard ratio [HR] = 0.741, 95% CI: 0.485–1.132, p = .166). Median OS was 18 months (95% CI: 4.1–31.9) in the PD-1 inhibitor group, compared with 14 months (95% CI: 12.1–15.9) in the carboplatin–gemcitabine group (HR = 0.731, 95% CI: 0.426–1.256, p = .257). The duration of response was significantly longer in the PD-1 inhibitor group than in the carboplatin–gemcitabine group (not reached vs. 9 months, p < .001). Treatment-related adverse events were less frequent in the PD-1 inhibitor group than in the carboplatin–gemcitabine group (57.1% vs. 77.3%). In conclusion, PD-1 inhibitors displayed promising efficacy with less toxicity and longer DOR in the first-line treatment of UTUC in patients ineligible for cisplatin-based chemotherapy.

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Introduction

Upper tract urothelial carcinoma (UTUC), defined as a primary tumor located in the pelvis or ureter, is a rare malignant disease with an annual morbidity of 2 per 100,000[1]. UTUC accounts for only 5%–10% of urothelial carcinoma in the western world, but the morbidity rate is higher in China at approximately 9%–30%.[1] The biological and clinical characteristics of UTUC differ from those of bladder carcinoma.[2,3] Almost two-thirds of UTUC patients have muscle invasive disease, and 9% present with metastasis at diagnosis.[4,5]

Because of its low morbidity, clinical trials specific for UTUC are challenging, and therefore high-level evidence is lacking. Treatment for UTUC is mostly inferred from trials for urothelial carcinoma, including cancers of both the upper tract and bladder.[6] Cisplatin-based chemotherapy has been recommended as the first-line treatment for metastatic UTUC in National Comprehensive Cancer Network and European Association of Urology guidelines due to an overall survival benefit of about 15 months.[7] However, around half of all real-world patients are ineligible for cisplatin treatment because of impaired renal function caused by nephroureterectomy, relatively advanced age, and chronic kidney disease.[8,9] Hence, although carboplatin-based chemotherapy is less effective, better tolerance support for its used in patients unable to receive cisplatin.[10]

The advent of immunotherapy, especially checkpoint inhibitors, has changed the paradigm of treatment for multiple malignancies including urothelial carcinoma.[11] Several programmed cell death (PD)-1/programmed cell death ligand (PD-L)1 inhibitors have been approved in the second-line setting because of their longer duration of response (DOR) and modest toxicity as

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compared with conventional chemotherapies such as docetaxel, paclitaxel, and vinblastine.[12,13] However, the situation is more complicated in the first-line setting. Although two phase II trials of PD-1/PD-L1 inhibitors showed objective response rates of 24%–28% and median overall survival times of 11.3–15 months for chemo-naïve and cisplatin-ineligible patients,[14,15] two subsequent phase III trials failed to reach their primary endpoint, thus limiting the PD-1/PD-L1 inhibitor indications in the first-line setting.[16,17] Additionally, UTUC patients comprised only 20%–25% of the total enrollment in the two phase III trials, and subgroup analysis of IMvigor130 showed a median progression-free survival time of 6.2 months and an median overall survival time of 13.5 months in UTUC patients treated with platinum combined with gemcitabine.[18] Thus far, it remains unknown which therapy is the optimal choice for patients with metastatic UTUC who are cisplatin-ineligible.

Here, we present a retrospective, multicenter, two-arm study that investigated the efficacy and safety of PD-1 inhibitors and carboplatin plus gemcitabine as the first-line treatment of UTUC patients who were chemo-naïve and cisplatin-ineligible.

Materials and methods

Patients

We retrospectively collected data from patients who had been diagnosed with metastatic UTUC, including those with cancers of the pelvis and ureter, in nine institutions between 2018 and 2021. Only those who met at least one of the following criteria and were assessed as cisplatin-ineligible were included: an Eastern Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance (calculated or measured) <60 mL/min, grade 2 audiometric hearing loss, grade 2 peripheral neuropathy, or New York Heart Association Class III heart failure. Other eligibility criteria included the receipt of at least one cycle of PD-1 inhibitor therapy or carboplatin combined with gemcitabine as first-line treatment for UTUC, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and at least one imaging study of the target lesion after treatment. Patients treated with neoadjuvant or adjuvant platinum-based chemotherapy with recurrence >12 months since completion of the therapy were permitted to be enrolled. Patients were excluded if they had received prior systemic chemotherapy or checkpoint inhibitors after first diagnosis of metastatic UTUC.

Ethics statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by ethics committee of Ren Ji Hospital and all other participating institutions (KY2021-102). The data was retrieved from electronic medical records of 9 participating institutions and informed consent was obtained from the participants involved.

Treatment and procedures

For cisplatin-ineligible patients with metastatic UTUC, PD-1 inhibitors or carboplatin-based chemotherapy served as the first-line treatment according to the guideline of the Chinese Society of Clinical Oncology. The treatment decision between PD-1 inhibitors or carboplatin plus gemcitabine depended on the preference of both the patients and physicians at each institution. Immune checkpoint inhibitors used in this study were as follows: tislelizumab (n = 30, 42.9%), toripalimab (n = 24, 34.3%), pembrolizumab (n = 9, 12.9%), nivolumab (n = 3, 4.3%), sintilimab (n = 2, 2.8%), and camrelizumab (n = 2, 2.8%). Patients were treated with PD-1 inhibitors by intravenous infusion of tislelizumab 200 mg, toripalimab 240 mg, pembrolizumab 200 mg, or sintilimab 200 mg once every 3 weeks, or with camrelizumab 200 mg and nivolumab 240 mg once every 2 weeks. Carboplatin was dosed in mg (5× [glomerular filtration rate + 25]), and given intravenously over 1 h on day 1, followed by gemcitabine 1,000 mg/m^2 intravenously over 30 min on days 1 and 8 every 3 weeks. Dose reduction was performed according to the manufacturer's instructions to manage adverse events (AEs). Treatment was continued until disease progression, intolerable toxicities, or death.

Assessments

PD-L1 expression was assessed in formalin-fixed tumor samples at individual centers and re-reviewed by a pathologist. Radiological evaluation was performed by the investigators at each institution via computed tomography and/or magnetic resonance imaging of the abdomen, chest, and brain, as well as bone scintigraphy, prior to the start of treatment and every 2–3 months thereafter according to RECIST 1.1. PFS was defined as the time from the start of treatment to disease progression or death from any cause. OS was defined as the time from the first treatment to death from any cause. The grade of AEs was recorded according to the Common Terminology Criteria for Adverse Events, version 5.0. All data were reviewed by two independent investigators.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 and GraphPad Prism 8 software. Categorical variables were compared using the chi-squared test. Continuous variables were compared using the unpaired *t*-test. Response rate was compared using the chi-squared test. OS and PFS were estimated using the Kaplan–Meier method. The difference between arms in OS and PFS were calculated using a stratified log-rank test. The evaluated prognostic variables included the type of first-line therapy, age, gender, ECOG, estimated glomerular filtration rate (eGFR), history of prior nephroureterectomy, location of metastases, histologic type, and Bajorin risk groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with a stratified Cox proportional-hazards model. P-values ≤0.05 were considered statistically significant.

Results

Patients and treatment

Between 2018 and 2021, a total of 182 UTUC patients were screened, of whom 123 met the inclusion criteria and were eligible for further analysis. Patient characteristics are shown in Table 1. A total of 70 patients received PD-1 inhibitors as first-line treatment, and 53 received gemcitabine in combination with carboplatin. Median follow-up time for these groups was 17 months.

We observed a slightly higher rate of lymph node metastasis in the PD-1 inhibitor group than in the carboplatin–gemcitabine group (50.0% vs. 41.5%, p = .350). The proportion of patients who received perioperative systemic therapy during prior nephroureterectomy, including neoadjuvant chemotherapy (4.3% vs. 1.9%, p = .818), adjuvant chemotherapy (22.9% vs. 28.3%, p = .491), and adjuvant radiotherapy (2.9% vs. 5.7%, p = .750). Regarding other differences, 18% of patients receiving PD-1 inhibitors were older than 80 years, compared with only 1.9% of patients receiving carboplatin–gemcitabine (p = .009). More patients in the carboplatin–gemcitabine group received prior nephroureterectomy (83.0% vs. 64.3%, p = .021). More patients in the PD-1 inhibitor group had primary tumors in the renal pelvis (50.9% vs. 32.1%, p = .046). In addition, approximately 40% of patients in the PD-1 inhibitor group were evaluated for tumor PD-L1 expression, which was ≥1% in 18.6% of patients, whereas the level of PD-L1 expression was unknown in the carboplatin–gemcitabine group.

ORR

As shown in Table 2, ORRs were 38.6% in the PD-1 inhibitor group and 41.5% in the carboplatin–gemcitabine group. Complete response rates were 2.9% and 3.8%, respectively. For patients with liver metastasis, a higher response rate was recorded in the carboplatin–gemcitabine group as compared with that in the PD-1 inhibitor group (45.5% vs 25%). In the PD-1 inhibitor group, patients with tumor PD-L1 expression ≥1% achieved an ORR of 46.2%, whereas the ORR was 26.7%

Table 1. Baseline clinical characteristics of UTUC patients.

Characteristic	PD-1 antibody Group(N = 70)	GC chemotherapy Group(N = 53)	P-value
Age, years (Median, Range)	69(40–91)	64(41–81)	0.429
Age≥80 years	13(18.6%)	1(1.9%)	0.009
Male Sex	40(60.0%)	37(69.8%)	0.150
ECOG			0.840
0–1	41(58.6%)	32(60.4%)	
≥2	29(41.4%)	21(39.6%)	
Prior nephroureterectomy	45(64.3%)	44(83.0%)	0.021
Perioperative therapy			
Neoadjuvant chemotherapy	3 (4.3%)	1 (1.9%)	0.818
Adjuvant therapy			
Chemotherapy	16 (22.9%)	15 (28.3%)	0.491
Radiotherapy	2 (2.9%)	3 (5.7%)	0.750
Metastatic disease			0.350
Visceral sites	35(50.0%)	31(58.5%)	
Liver	16(22.9%)	11(20.8%)	
Bone	12(17.1%)	14(26.4%)	
LN only	35(50.0%)	22(41.5%)	
Primary tumor site			0.078
Renal pelvis	35(50.9%)	17(32.1%)	
Ureter	32(45.7%)	35(66.0%)	
Both	3(4.3%)	1(1.9%)	
Reason unfit for cisplatin therapy			0.994
ECOG≥2	15(21.4%)	11(20.8%)	
eGFR <60	30(42.9%)	23(43.4%)	
Hearing loss	7(10.0%)	5(9.4%)	
Peripheral neuropathy	4(5.7%)	2(3.8%)	
Renal impairment and ECOG ≥2	14(20.0%)	10(18.9%)	
PD-L1 expression			
<1%	15(21.4%)	-	
≥1%	13(18.6%)	-	
unknown	42(60.0%)	53(100.0%)	
eGFR			0.946
≥60	26(37.1%)	20(37.7%)	
<60	44(62.9%)	33(62.3%)	
Histology			0.900
Pure Urothelial	60(85.7%)	45(84.9%)	
Mixed Urothelial	10(14.3%)	8(15.1%)	
Bajorin risk groups			0.905
0	19(27.1%)	15(28.3%)	
1	37(52.9%)	26(49.1%)	
2	14(20.0%)	12(22.6%)	

UTUC: upper tract urothelial carcinoma ECOG: Eastern Cooperative Oncology Group
PD-L1: programmed-death ligand 1 GC: gemcitabine/carboplatin
GFR: glomerular filtration rate ICI: immune checkpoint inhibitors

Table 2. Objective response, and duration of response in all treated patients.

Subgroup	PD-1 antibody Group(N = 70)	GC chemotherapy Group(N = 53)	P-value
Confirmed objective response	27/70(38.6%)	22/53(41.5%)	0.742
Complete response	2/70(2.9%)	2/53(3.8%)	
Partial response	25/70(35.7%)	20/53(37.7%)	
Stable disease	16/70(22.9%)	19/53(35.8%)	
Progressive disease	27/70(38.6%)	12/53(22.6%)	
Duration of response, months	NR(NR-NR)	9(7.8–10.2)	<0.001
Age>80 years	5/13(38.5%)	1/1(100.0%)	
Metastatic disease			
Visceral sites	11/35(31.4%)	12/31(38.7%)	0.656
Liver	4/16(25.0%)	5/11(45.5%)	0.411
LN only	16/35(45.7%)	10/22(45.5%)	0.875
eGFR			
≥60	10/26(38.5%)	7/20(35.0%)	0.809
30–60	15/42(35.7%)	15/33(45.5%)	0.440
<30	2/3(66.7%)	0/0(0.0%)	-
PDL1 expression			
<1%	4/15(26.7%)	-	
≥1%	6/13(46.2%)	-	
Unknown	17/42(40.4%)	22/53(41.5%)	
Histology			
Pure Urothelial	23/60(38.3%)	20/45(44.4%)	0.529
Mixed Urothelial	4/10(40.0%)	2/8(25.0%)	0.638
Bajorin risk groups			
0	8/18(44.4%)	7/15(46.7%)	0.746
1	14/38(36.8%)	11/26(42.3%)	0.801
2	5/14(35.7%)	4/12(33.3%)	1.000

for patients with tumor PD-L1 expression ≤1%. Moreover, the DOR was significantly longer in the PD-1 inhibitor group (median DOR: not reached) than in the carboplatin–gemcitabine group (median DOR: 9.0 months, 95% CI: 7.8–10.2,) ($p < .001$, Table 2).

PFS and OS

No significant difference was found with respect to median PFS between patients in the PD-1 inhibitor group and carboplatin–gemcitabine group (5.0[95%CI, 2.0–8.0] versus 7.0[95%CI, 5.8–8.2] months, respectively; HR = 0.741, 95% CI: 0.485–1.132, p = .166; Figure 1a). The median OS was also comparable between the two groups (18.0[95% CI, 4.1–31.9] versus 14.0[95%CI, 12.1–15.9] months, respectively; HR = 0.731, 95% CI: 0.426–1.256, p = .257; Figure 1b). No significant difference was found among all subgroups with respect to PFS (Figure 2a) and OS (Figure 2b). In the PD-1 inhibitor group, patients with PD-L1 expression ≥1% had a significantly longer OS compared with patients in the carboplatin–gemcitabine group (median OS, NR versus 14 months, HR = 0.272, 95% CI: 0.081–0.913, p = .035) (Figure 1c). Univariate and multivariate analyses findings are listed in Table 3. Multivariate analysis showed that visceral metastasis was the only independent risk factor for poor OS ($p < .001$).

Safety

The overall safety profile is shown in Table 4. In the PD-1 inhibitor group, treatment-related adverse events of any grade occurred in 57.1% of patients, and 10% of patients experienced adverse events of grade 3 or higher. The most common treatment-related adverse events included rash (11.4%), pruritus (11.4%), fatigue (10%), and diarrhea (7.1%). Toxicity was much higher in the carboplatin–gemcitabine group, with treatment-related adverse events of any grade occurring in 77.3% of patients, and adverse events of grade 3 or higher occurring in 37.7% of patients. A different toxicity profile than predicted

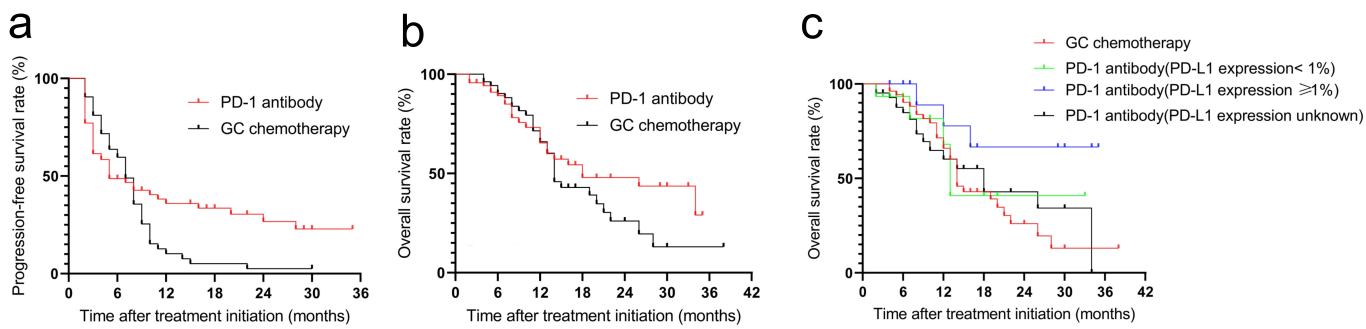

Figure 1. PFS (a) and OS (b) of patients with advanced UTUC treated with ICI and carboplatin–gemcitabine; subgroup analysis of OS in advanced UTUC patients treated with ICI and carboplatin–gemcitabine according to PD-L1 expression (c).

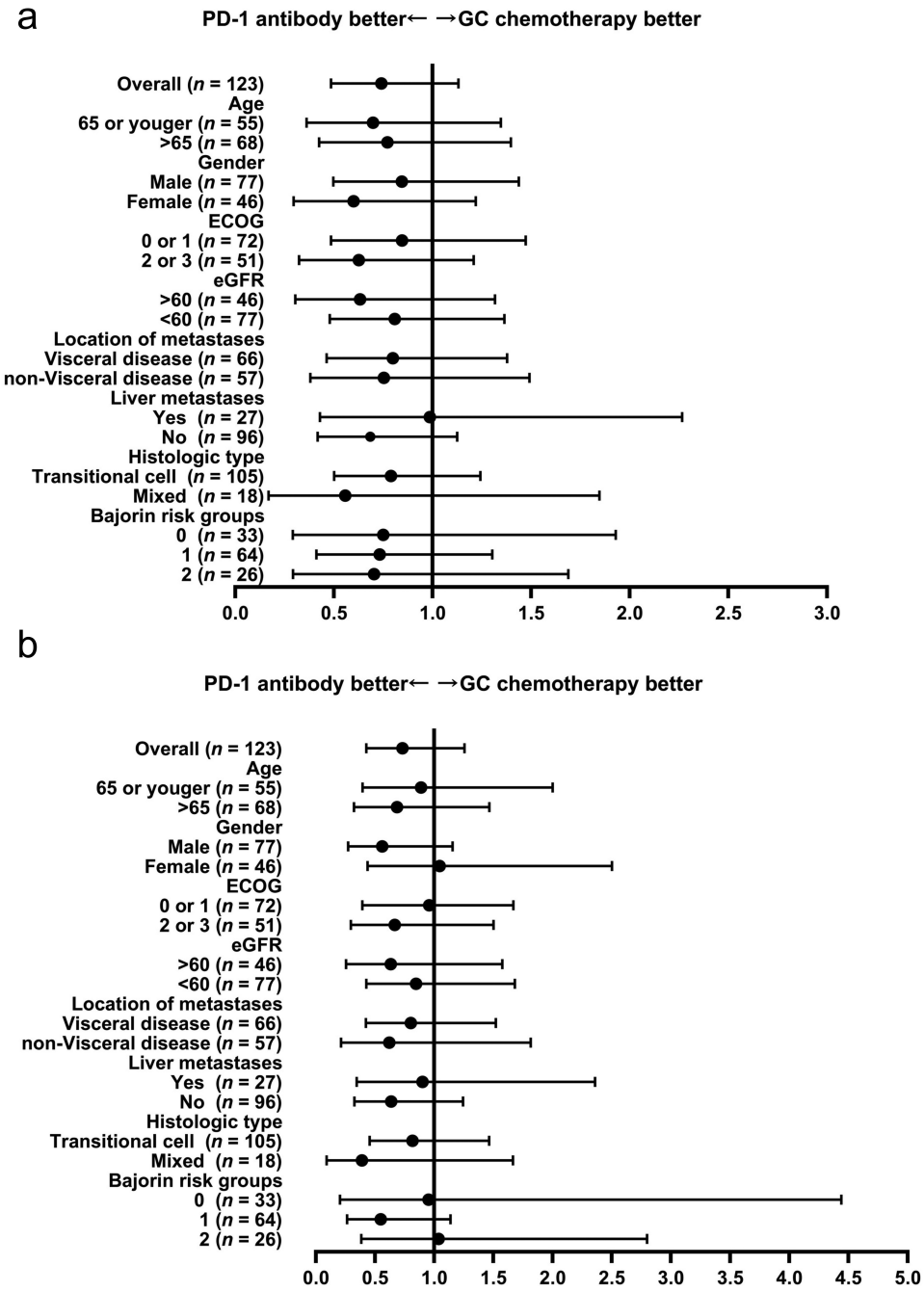

Figure 2. Subgroup analysis of PFS (a) and OS (b) of advanced UTUC patients treated with ICI and carboplatin–gemcitabine.

was observed in the carboplatin–gemcitabine group. The most common treatment-related adverse events included neutropenia (75.5%), leukopenia (71.7%), thrombocytopenia (47.2%), and nausea (45.3%). No treatment-related deaths were recorded in either group. Use of PD-1 inhibitors appeared to be more tolerable, with only 4.3% of patients discontinuing treatment because of adverse events in the PD-1 inhibitor group compared with 18.9% of patients in the carboplatin–gemcitabine group.

Discussion

Our study evaluated the efficacy of PD-1 inhibitors and carboplatin combined with gemcitabine as first-line treatments for advanced UTUC patients who were ineligible for cisplatin-based chemotherapy. Patients in the PD-1 inhibitor group had an ORR of 38.6%, with a median PFS of 5.0 months and a median OS of 18 months. In comparison, patients receiving carboplatin–gemcitabine had an ORR of 41.5%, with a median PFS of 7.0 months and median OS of 14 months.

In cohort 1 of the phase 2 IMvigor 210 trial, atezolizumab was associated with an ORR of 39% among cisplatin-ineligible patients with UTUC, who comprised 28% of the total population.[14] However, the ORR was decreased to 17% in the remaining 72% of patients with lower tract disease. In line with the results of the UTUC subgroup of IMvigor 210, our study observed a similar ORR of 38.6% in the PD-1 inhibitor group, which could indicate a better response to PD-1 inhibitors in the

Table 3. Univariate and multivariate analysis of associations of various parameters with OS during GC and ICI treatment.

Variable	Univariate analysis HR (95% CI)	P-value	Multivariate analysis HR (95% CI)	P-value
Age (>65 vs≤65 years)	0.890 (0.512–1.547)	0.68	-	-
Gender (male vs. female)	0.965 (0.557–1.670)	0.898	-	-
ECOG (≥2vs.<2)	0.938 (0.546–1.612)	0.818	-	-
eGFR (<60vs.≥60)	0.855 (0.494–1.482)	0.577	-	-
Prior nephroureterectomy (yes vs. no)	0.910 (0.505–1.642)	0.754	-	-
Metastatic sites (visceral vs. LN only)	3.196 (1.707–5.985)	<0.001	3.196 (1.707–5.985)	<0.001
Liver metastasis (yes vs. no)	2.127 (1.203–3.760)	0.009	-	-
Histological subtype (Mixed Urothelial vs. Pure Urothelial)	1.206(0.568–2.560)	0.626	-	-
Type of first-line therapy (ICI vs. GC treatment)	0.731 (0.426–1.256)	0.257	-	-
Bajorin risk groups				
0	1	0.021	-	-
1	1.994 (0.874–4.551)	0.101	-	-
2	3.392 (1.403–8.204)	0.007	-	-

Table 4. Treatment-related adverse events.

	PD-1 antibody Group(N = 70)		GC chemotherapy Group(N = 53)	
Adverse event	Any grade	Grade 3–4	Any grade	Grade 3–4
Any event	40(57.1%)	7(10.0%)	41(77.3%)	20(37.7%)
Event leading to discontinuation of treatment	3(4.3%)	3(4.3%)	10(18.9%)	6(11.3%)
Fatigue	7(10.0%)	1(1.4%)	12(22.6%)	2(3.8%)
Pruritus	8(11.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Diarrhea	5(7.1%)	1(1.4%)	4(7.5%)	0(0.0%)
Decreased appetite	5(7.1%)	0(0.0%)	8(15.0%)	0(0.0%)
Rash	8(11.4%)	2(2.9%)	6(11.3%)	0(0.0%)
Hypothyroidism	4(5.7%)	0(0.0%)	0(0.0%)	0(0.0%)
Hyperthyroidism	2(2.9%)	0(0.0%)	0(0.0%)	0(0.0%)
Nausea	3(4.3%)	0(0.0%)	24(45.3%)	1(1.9%)
Pyrexia	3(4.3%)	0(0.0%)	1(1.9%)	0(0.0%)
ALT increased	4(5.7%)	1(1.4%)	3(5.7%)	0(0.0%)
AST increased	3(4.3%)	1(1.4%)	2(3.8%)	0(0.0%)
Anemia	4(5.7%)	1(1.4%)	16(30.2%)	1(1.9%)
Interstitial pneumonia	3(4.3%)	1(1.4%)	0(0.0%)	0(0.0%)
Leukopenia	4(5.7%)	0(0.0%)	38(71.7%)	13(24.5%)
Neutropenia	2(2.9%)	0(0.0%)	40(75.5%)	14(26.4%)
Lipase increase	4(5.7%)	0(0.0%)	0(0.0%)	0(0.0%)
Thrombocytopenia	2(2.9%)	0(0.0%)	25(47.2%)	8(15.1%)
Hypercholesteremia	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Myocarditis	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Bilirubin increase	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Adrenal insufficiency	1(1.4%)	0(0.0%)	0(0.0%)	0(0.0%)
Infection	0(0.0%)	0(0.0%)	4(7.5%)	1(1.9%)
Peripheral sensory neuropathy	0(0.0%)	0(0.0%)	2(3.8%)	0(0.0%)

UTUC population. Meanwhile, UTUC is more frequently observed in the Asian population than in the Caucasian population. In several areas of East Asia, including China, aristolochic acid is one of the leading causes of UTUC, and it is associated with a higher tumor mutation burden, which may result in a better response to PD-1 inhibitors. The 38.6% ORR in the PD-1 inhibitor group was also comparable with the 41.5% ORR in the carboplatin–gemcitabine group. Furthermore, the ORR reached 46.2% in patients with PD-L1 expression ≥1 in the PD-1 inhibitor group, which was consistent with a previous study in which the predictive value of PD-L1 status was confirmed in UC patients treated with PD-1 inhibitors or PD-L1 inhibitors.[19] This result was promising because PD-1 inhibitor monotherapy failed to prove its superiority to platinum-based chemotherapy in the first-line treatment of urothelial carcinoma, with an ORR of 30% for the pembrolizumab group and 45% for the chemotherapy group in the KEYNOTE-361 trial.[17] It is worth noting that in the PD-1 inhibitor group, the ORR was 45.7% among patients with lymph node metastasis, versus 31.4% among patients with visceral metastasis. In addition, an ORR of 25% was observed in patients with liver metastasis in the PD-1 inhibitor group. Although the ORR of patients UTUC and liver metastasis who received PD-1 inhibitors was higher than that of previous studies,[20,21] several factors, including the limited sample size, heterogeneity of UTUC and Asian populations, and retrospective design, should not be neglected. Regardless, comparable ORRs were observed in the carboplatin–gemcitabine group in the current study and in prior research, indicating that carboplatin-based chemotherapy might be a better choice for patients with visceral metastasis, especially liver metastasis.

Fibroblast growth factor receptor 3 (FGFR3) has been identified as one of the most commonly mutated genes (including TERT promoter, KMT2D, CDKN2A, and TP53) in UTUC.[22] FGFR3 alterations were also more frequent in UTUC than in lower tract disease.[23] Approximately half of all high-grade UTUCs and three-fourths of low-grade UTUCs feature such alterations. Such alterations are associated with better survival and lower tumor grades. Earlier findings in bladder cancer indicated that pathological FGFR3 alterations such as the S249C mutation and TACC3 fusion negatively affect the response to immune checkpoint inhibitors. However, their value was examined using data derived from IMvigor 210 and CheckMate-275.[24,25] The response rate was similar between patients with wild-type and mutant FGFR3.[26]

PFS was similar between the two groups in our study, although a longer albeit non-significant OS benefit was observed for PD-1 inhibitor treatment in our study (18 months versus 14 months, respectively, p = .245). The OS of both groups was much longer than seen in the EORTC 30986 study, in which carboplatin–gemcitabine achieved a median OS of 9.3 months.[27] The prolonged OS seen in our study might be associated with the improved healthcare management and the application of immune checkpoint inhibitors in the second-line setting where conventional chemotherapies such as docetaxel and paclitaxel show poor OS and notable toxicity.[12,13]

Of note, longer OS was observed in the PD-1 inhibitor group among patients with ≥1% PD-L1 expression than in the carboplatin–gemcitabine group, although the PD-L1 status was not evaluable in the latter group. While no significant difference was found in the PFS or OS of the total population between the two groups, crossovers were present in both Kaplan–Meier curves, and durable PFS and OS benefits were observed in the PD-1 inhibitor group over the carboplatin–gemcitabine group. This could be explained by the longer DOR in patients with an objective response after receiving PD-1 inhibitor therapy. The median DOR was not reached in the PD-1 inhibitor group in our study, with a median follow-up time of 17 months, while the tumor response lasted for about 9 months in the carboplatin–gemcitabine group (p < .001). Patients receiving carboplatin–gemcitabine therapy did not achieve a durable PFS or OS benefit, although more patients might achieve a tumor response at the early stage. The high ORR and long-lasting DOR reported in our study indicate that PD-1 inhibitors are potent treatment options and promising alternatives to carboplatin–gemcitabine in the treatment of patients who are cisplatin-ineligible, especially in patients with PD-L1 expression ≥1%.

The treatment of UTUC patients is challenging because most patients have hydronephrosis or an impaired renal function status, especially those who have undergone radical nephroureterectomy,[28] which makes them vulnerable to cytotoxic chemotherapy causing renal toxicity. Moreover, hydronephrosis is associated with a poor oncological outcome,[29–31] stressing the importance of exploring other regimens in addition to platinum-based chemotherapy. PD-1/PD-L1 inhibitors have been shown to be well-tolerated in patients with an impaired renal function. In the KEYNOTE-052 trial, almost half of all patients were classified as cisplatin-ineligible because of renal dysfunction.[21] In cohort 1 of the IMvigor 210 trial, atezolizumab was associated with a modest renal impairment, with renal failure occurring in only 2% of the total enrollment.[32] In our study, 60% of patients in the PD-1 inhibitor group presented with an eGFR of 30–60 ml/min, although the ORR was inferior to that seen in the carboplatin–gemcitabine group (35.7% versus 45.5%, respectively). Three patients with an eGFR of <30 ml/min who were unfit for any platinum-based chemotherapy received PD-1 inhibitors in the PD-1 inhibitor group. Such patients usually have poor clinical outcomes,[33] nevertheless two of the three achieved an objective response in our study. This is consistent with previous findings,[21,32] indicating that PD-1 inhibitors are ideal agents for patients with impaired renal function.

Considering the potential cumulative toxicities, most patients discontinue first-line platinum-based chemotherapy after around six cycles.[34] The median time to progression was approximately 2 months with best supportive care after four to six cycles of platinum-based chemotherapy.[35] In our study, fewer treatment-related adverse events of ≥grade 3 occurred in patients in the PD-1 inhibitor group compared with those in the carboplatin–gemcitabine group (10% versus 37.7%, respectively). Thirteen patients in the PD-1 inhibitor group were aged over 80 years, of whom five achieved an objective response. Our findings therefore show that PD-1 inhibitors are effective and safe in the older population.

To our knowledge, this is the first retrospective, real-world, multicenter study specific for UTUC that compares PD-1 inhibitors and carboplatin–gemcitabine combination chemotherapy in the treatment of patients who are cisplatin-ineligible. This study had several limitations. First, the retrospective study design increased the potential bias concerning population collection. Several differences in baseline characteristics exist between the two groups, including age, prior history of nephroureterectomy, and the primary tumor site. Second, only 40% samples were available to test PD-L1 expression in the PD-1 inhibitor group, and the PD-L1 status was unknown for all patients in the carboplatin–gemcitabine group. Thus, there could be heterogeneity regarding PD-L1 expression between the two groups. Third, the sample size was relatively small, with 70 patients in the PD-1 inhibitor group and 53 in the carboplatin–gemcitabine group. Therefore, although the ORR, PFS, and OS observed here are consistent with those seen in previous phase II trials, our results should be confirmed in randomized controlled clinical trials of UTUC patients.

In summary, we performed a retrospective, real-world study to evaluate the efficacy and safety of PD-1 inhibitors and carboplatin combined with gemcitabine in the first-line treatment of UTUC patients who were unfit for cisplatin-based chemotherapy. Our results show that PD-1 inhibitors provide a comparable ORR, PFS, and OS to carboplatin–gemcitabine, with lower toxicity and a longer DOR. PD-1 inhibitors are therefore promising alternatives to carboplatin-based chemotherapy for UTUC patients who are cisplatin-ineligible.

Abbreviations:

CR, complete response
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
eGFR, estimated glomerular filtration rate
ICI, immune checkpoint inhibitor
ORR, objective response rate
OS, overall survival
PD, progressive disease
PD-1, programmed cell death 1
PD-L1, programmed cell death ligand 1
PFS, progression-free survival
PR, partial response
SD, stable disease
UTUC, upper tract urothelial carcinoma

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Disclosure statement

The authors report no conflict of interest.

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Data Availability Statement

Jiwei Huang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data that support the findings of this study are available from the corresponding authors upon request.

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