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First-line Immune Checkpoint Inhibitor Versus Immune Checkpoint Inhibitor With Chemotherapy for Cisplatin-ineligible Metastatic Urothelial Carcinoma: Evidence From a Real-world, Multicenter Analysis

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Summary: Immune checkpoint inhibitors (ICIs) are widely used for first-line cisplatin-ineligible patients with metastatic urothelial carcinoma (mUC). However, whether to use ICIs as monotherapy or in combination with chemotherapy is still uncertain. We retrospectively analyzed cisplatin-ineligible patients with mUC who underwent first-line ICI monotherapy or ICI plus chemotherapy at 2 medical centers in Taiwan from 2016 to 2021. We calculated the objective response rate, progression-free survival, and overall survival (OS) using the Kaplan-Meier method and Cox regression model for multivariable analysis. In total, 130 patients were enrolled and categorized into 2 groups: an ICI monotherapy group [immunotherapy (IO), n = 101] and an ICI plus noncisplatin chemotherapy group [immunotherapy and chemotherapy (IC), n = 29]. The median OS of patients in the IO and IC groups was 19.5 and 9.7 months ($P = 0.33$). Among patients with high programmed cell death ligand-1–expressing tumors, the median OS was significantly prolonged in the IO group compared with the IC group (not reached vs. 6.3 mo, $P = 0.02$). First-line ICI monotherapy demonstrated robust antitumor activity in cisplatin-ineligible patients with mUC. Combining noncisplatin chemotherapy with ICI did not improve clinical outcomes.

Key Words: urothelial carcinoma, immunotherapy, real-world evidence

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Before the introduction of immune checkpoint inhibitors (ICIs) for chemotherapy-refractory metastatic urothelial carcinoma (mUC), platinum-based chemotherapy was the standard first-line treatment.[1–3] The most common regimens, such as gemcitabine/cisplatin (GC) and methotrexate, vinblastine, doxorubicin, and cisplatin, yielded a high objective response rate (ORR) and median overall survival (OS) of 14 months.[4,5] However, the duration of chemotherapy response was not indefinite, and the disease eventually progressed, resulting in patient death. The treatment paradigm has shifted recently as ICIs have been widely investigated for clinical efficacy in many cancers, including platinum-refractory mUC.[6–8] mUC often affects older adults with more comorbidities and poor performance status (PS), limiting the utility of cisplatin-based chemotherapy. Several studies have demonstrated that using ICIs for cisplatin-ineligible patients with mUC is safe and effective.[9–11] Because of these promising results, 5 programmed cell death (PD)-/PD-L1 inhibitors have been approved by the US Food and Drug Administration and European Medicines Agency for the treatment of patients with mUC who are refractory to platinum-based chemotherapy or ineligible for first-line cisplatin chemotherapy.

Although several large, prospective studies investigating the survival outcomes of chemotherapy with or without ICIs have yielded disappointing results, the efficacy and survival outcomes of ICIs monotherapy compared with ICIs plus chemotherapy have not been reported in detail.[12–14] In the IMvigor-130 study, the ORR of patients who received atezolizumab with chemotherapy was higher than that of patients receiving atezolizumab monotherapy (47% vs. 23%). The median OS with atezolizumab/chemotherapy and atezolizumab monotherapy was 16.0 and 15.7 months, respectively. Notably, the median duration of response (DOR) for atezolizumab was not reached (NR) and was much higher than 8.5 months in the atezolizumab/chemotherapy group, suggesting a persistent and durable tumor-shrinking effect. Similar results were observed in the KEYNOTE-361 study; the ORR was higher for patients receiving pembrolizumab/chemotherapy (54.7%) than for patients receiving pembrolizumab monotherapy (30.3%). However, this was not observed for OS (17.0 vs. 15.6 mo), and the median DOR was higher in the pembrolizumab monotherapy group (28.5 mo) than in the pembrolizumab/chemotherapy group (8.5 mo). Of note, neither the IMvigor-130 nor the KEYNOTE-361 studies were designed to test the superiority of ICIs combined with chemotherapy over ICIs alone, suggesting that the post hoc analysis of the 2 groups did not have sufficient power to support the hypothesis.

A recent study demonstrated that maintenance avelumab improved OS in responders to first-line GC or gemcitabine/carboplatin chemotherapy; however, the optimal treatment strategy for cisplatin-ineligible patients, with the question posed as whether ICIs and chemotherapy should be administrated simultaneously or in sequence, is still unknown.[15–17] To the best of our knowledge, no real-world study has reported the efficacy of the combination of ICIs and noncisplatin chemotherapy. Therefore, we conducted this retrospective study to illustrate our real-world experience treating locally advanced or mUC with ICIs with or without chemotherapy.

MATERIALS AND METHODS

Patients and Treatments

We retrospectively reviewed medical records and analyzed relevant clinical parameters at 2 academic medical centers: Kaohsiung Chang Gung Memorial Hospital and Linkou Chang Gung Memorial Hospital in Taiwan. All patients were histopathologically diagnosed with urothelial carcinoma of the renal pelvis, ureter, or urinary bladder. All patients received at least 1 cycle of ICI therapy (pembrolizumab, atezolizumab, nivolumab, durvalumab, or avelumab), with or without nonplatinum-based chemotherapy as first-line treatment. Patients who received single-agent or combination chemotherapy were included. Patients who received an ICI with tyrosine kinase inhibitors or any therapeutic targeting agents were excluded. The study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201901248B0).

Clinical Data and Response Evaluation

The following demographic data of the patients at the time of the first cycle of immunotherapy (IO) was extracted from medical records: age, Eastern Cooperative Oncology Group (ECOG), laboratory data, Bajorin risk score, and expression of PD-L1. Immunohistochemistry staining of PD-L1 was detected by the 22C3 antihuman PD-L1 antibody and interpreted by a certificated pathologist (T.T.L.) using the combined positivity score. The presence of visceral organ metastasis was assessed by computed tomography scan or magnetic resonance imaging. The choice of a systemic therapy regimen for each patient was based on the clinical physician's decision.

Treatment response was assessed by clinical physicians using the RECIST criteria version 1.1. Progression-free survival (PFS) was the interval between the start date of systemic therapy and the date of established progression or death. OS was the interval between the start date of therapy and the date of death from any cause or the date the patient was censored.

Statistics

Differences in baseline characteristic data and treatment response between the 2 groups were analyzed using χ^2 and Fisher exact tests. Survival analysis was calculated using the Kaplan-Meier method and tested by the log-rank test. Cox proportional hazards regression was applied to prognostic factors. Only the factors that showed statistical significance or borderline significance ($P < 0.1$) in the univariate analysis were added stepwise to the multivariate analysis. All tests were 2 tailed, and a P-value <0.05 was considered statistically significant in all analyses. Hazard ratios (HR) were calculated and expressed along with 95% confidence intervals (CIs). The statistical analysis was performed using SPSS Statistics version 25 (IBM Corporation) and GraphPad Prism version 8.21 (GraphPad Software, La Jolla, CA).

RESULTS

Patient Characteristics and Treatment Regimens

From April 2016 through May 2021, 130 patients with mUC were enrolled, with 101 patients in the ICI monotherapy (IO) group and 29 patients in the ICI plus

TABLE 1. Clinicopathologic Characteristics of All Patients

	All, n (%)	IO, n (%)	IC, n (%)	P
Age (y)	—	—	—	0.96
< 60	22 (16.9)	17 (16.8)	5 (17.2)	—
≥ 60	108 (83.1)	84 (83.2)	24 (82.2)	—
Sex	—	—	—	0.53
Female	55 (42.3)	41 (40.6)	14 (48.3)	—
Male	75 (57.7)	60 (59.4)	15 (51.7)	—
ECOG	—	—	—	0.48
0–1	96 (73.8)	76 (75.2)	20 (69.0)	—
≥ 2	34 (26.2)	25 (24.8)	9 (31.0)	—
Renal function (mL/min)	—	—	—	0.64
CCr ≥ 60	38 (29.2)	31 (30.7)	7 (24.1)	—
CCr < 60	92 (70.8)	70 (69.3)	22 (75.9)	—
Primary site	—	—	—	0.99
Bladder	57 (43.8)	44 (43.6)	13 (44.8)	—
Upper tract	73 (56.2)	57 (56.4)	16 (55.2)	—
Visceral metastasis	—	—	—	0.09
No	68 (52.3)	57 (56.4)	11 (37.9)	—
Yes	62 (47.7)	44 (43.6)	18 (62.1)	—
Lymph node metastasis	—	—	—	0.50
No	42 (32.3)	31 (30.7)	11 (37.9)	—
Yes	88 (67.7)	70 (69.3)	18 (62.1)	—
Liver metastasis	—	—	—	0.59
No	107 (82.3)	84 (83.2)	23 (79.3)	—
Yes	23 (17.7)	17 (16.8)	6 (20.7)	—
Lung metastasis	—	—	—	0.36
No	91 (70.0)	73 (72.3)	18 (62.1)	—
Yes	39 (30.0)	28 (27.7)	11 (37.9)	—
Bone metastasis	—	—	—	0.28
No	105 (80.8)	84 (83.2)	21 (72.4)	—
Yes	25 (19.2)	17 (16.8)	8 (27.6)	—
WBC (×10³/μL)	—	—	—	0.26
< 10	93 (71.5)	73 (72.3)	20 (69.0)	—
≥ 10	33 (25.4)	25 (24.7)	8 (27.6)	—
Missing	4 (3.1)	3 (3.0)	1 (3.4)	—
NLR	—	—	—	0.13
< 5	73 (56.2)	57 (56.4)	16 (55.2)	—
≥ 5	49 (37.7)	37 (36.7)	12 (41.4)	—
Missing	8 (6.2)	7 (6.9)	1 (3.4)	—
Hemoglobin (g/dL)	—	—	—	0.58
≥ 10	78 (60.0)	63 (62.4)	15 (51.7)	—
< 10	48 (36.9)	35 (34.7)	13 (44.8)	—
Missing	4 (3.1)	3 (3.0)	1 (3.4)	—
Bajorin risk factor	—	—	—	0.37
0	55 (42.3)	46 (45.5)	9 (31.0)	—
1	59 (45.4)	43 (42.6)	16 (55.2)	—
2	16 (12.3)	12 (11.9)	4 (13.8)	—
PD-L1 (22C3)	—	—	—	0.78
< 10	45 (34.6)	36 (35.6)	9 (31.0)	—
≥ 10	34 (26.2)	25 (24.8)	9 (31.0)	—
Missing	51 (39.2)	40 (39.6)	11 (38.0)	—

CCr indicates clearance of creatinine; ECOG, Eastern Cooperative Oncology Group; IC, immunotherapy and chemotherapy; IO, immunotherapy; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand-1; WBC, white blood cell count.

chemotherapy [immunotherapy and chemotherapy (IC)] group. The median follow-up time was 21.8 months, and the median patient age was 72 years (range: 29–90 y). Seventy-five patients were male (57.7%) and 78 patients (56.2%) had upper tract urothelial carcinoma (UTUC). The baseline characteristics were not significantly different between groups (Table 1). The main reason patients were considered cisplatin-ineligible was creatinine clearance <60 mL/min (70.8%), followed by ECOG PS ≥ 2 (26.2%), hearing loss (15.4%), congestive heart failure or coronary artery disease (14.6%), and significant peripheral neuropathy (12.3%). All details concerning the reasons for cisplatin ineligibility are shown in Table 2.

Regarding the ICI regimen, anti-PD1 treatment (pembrolizumab or nivolumab) was the most common regimen in both the IO (57.4%) and IC (55.2%) groups. For patients receiving IC treatment, 14 (48.3%) patients received gemcitabine monotherapy, 12 (41.4%) received gemcitabine with carboplatin chemotherapy, and 3 patients received taxanes (Table 3).

Treatment Response and Survival Outcomes

Thirteen patients in the IO group and 1 in the IC group had a confirmed complete response (12.9% vs. 3.4%, $P = 0.15$). The partial response rates were not significantly different in the IC and IO groups (21.8% vs. 31.0%, $P = 0.33$). There were no significant differences between the IO and IC groups regarding ORR and disease control rate (DCR). Among patients with PD-L1-expressing tumors, the ORR in the IO group was significantly higher than in the IC group (64.0% vs. 22.2%, $P = 0.03$). However, there was no significant difference in ORR between the IO and IC groups for patients without PD-L1 expression. The treatment responses in the 2 groups are shown in Figure 1.

During follow-up, 68 deaths (58 events in the IO group and 10 in the IC group) occurred. The median OS of patients in the IO group was 19.5 months compared with 9.7 months in the IC group, although this difference was not significant ($P = 0.33$, Fig. 2A). The median PFS of patients in the IO and IC groups was 3.5 and 5.5 months, respectively ($P = 0.79$; Fig. 2B). For patients with high PD-L1-expressing tumors, the median OS significantly improved in the IO group compared with the IC group (NR vs. 6.3 mo; $P = 0.02$; Fig. 3A). However, OS differences were not observed between the 2 groups for patients with tumors with low PD-L1 expression (17.5 mo in IO vs. NR in IC; $P = 0.89$; Fig. 3B).

To further understand whether ICI with single or doublet chemotherapy was more effective, we analyzed the differences in ORR, PFS, and OS between 3 groups (IO, IC-single, and

TABLE 2. Reasons of Cisplatin Ineligibility

	n (%)
Chronic kidney disease (CCr <60 mL/min)*	92 (70.8)
ECOG ≥ 2	34 (26.2)
Heart failure or coronary artery disease	19 (14.6)
Hearing loss	20 (15.4)
Peripheral neuropathy	16 (12.3)
Others†	6 (4.6)

*Seven patients with end-stage renal disease (ESRD) were included.
†Three deep venous thrombosis/pulmonary embolism, 1 significant carotid stenosis, 1 vertebral artery dissection, 1 age > 90 years old.
CCr indicates clearance of creatinine; ECOG, Eastern Cooperative Oncology Group.

TABLE 3. Regimen of Systemic Treatment

	IO, n (%)	IC, n (%)
Immunotherapy		
Anti-PD1	58 (57.4)	16 (55.2)
Anti-PDL1	43 (42.6)	13 (44.8)
Chemotherapy		
Gemcitabine/carboplatin	—	12 (41.4)
Gemcitabine	—	14 (48.3)
Taxane*	—	3 (10.3)

*Two patients received docetaxel; 1 patient received paclitaxel.
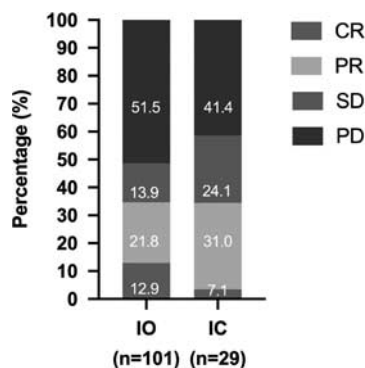IC indicates immunotherapy and chemotherapy; IO, immunotherapy; PD-L1, programmed cell death ligand-1.

IC-GCa). Patients in the IC-GCa group had the highest ORR (54.5%); ORR was 34.7% in the IO group and 22.2% in the IC-single group (Fig. 4). The IC-GCa group had a DCR of 90.9%, which was significantly superior to the DCRs of 48.5% in the IO group and 38.9% in the IC-single group ($P = 0.016$). The median OS of the IO, IC-single, and IC-GCa was 19.5 months, 6.3 months, and NR, respectively ($P = 0.11$; Fig. 5A). Patients in the IC-GCa groups had a significantly improved PFS compared with the IC-single group (10.9 vs. 2.7 mo, $P = 0.005$; Fig. 5B).

The other significant prognostic factors for OS revealed by the Kaplan-Meier analysis were ECOG PS ≥ 2, liver metastasis, bone metastasis, white blood cell count $\geq 10 \times 10^3/\mu L$, neutrophil-to-lymphocyte ratio (NLR) ≥ 5 and hemoglobin (Hb) <10 g/dL (Table 4). We performed a multivariate analysis using the Cox regression model to determine the independent prognostic roles of all variables. The independent predictors for OS were ECOG PS ≥ 2 (HR: 2.04, 95% CI, 1.18–3.53, $P = 0.01$), liver metastasis (HR: 2.63, 95% CI, 1.40–4.96, $P = 0.003$), leukocytosis (HR: 2.39, 95% CI, 1.24–4.63, $P = 0.01$), and Hb <10 g/dL (HR: 1.78; 95% CI, 1.00–3.18; $P = 0.05$).

Twenty-seven patients (20.7%) received subsequent therapy, including chemotherapy, IO, or others (Table 5). The distribution was not significantly different in the IC and IO groups (17.8% vs. 31.0%, $P = 0.12$).

DISCUSSION

In recent years, ICIs have led to a paradigm shift in treating platinum-refractory mUC and demonstrated efficacy in first-line cisplatin-ineligible patients with mUC.

FIGURE 1. Treatment responses of all patients in the IO and IC groups. CR indicates complete response; IC, immunotherapy and chemotherapy; IO, immunotherapy; PD, progressive disease; PR, partial response; SD, stable disease.
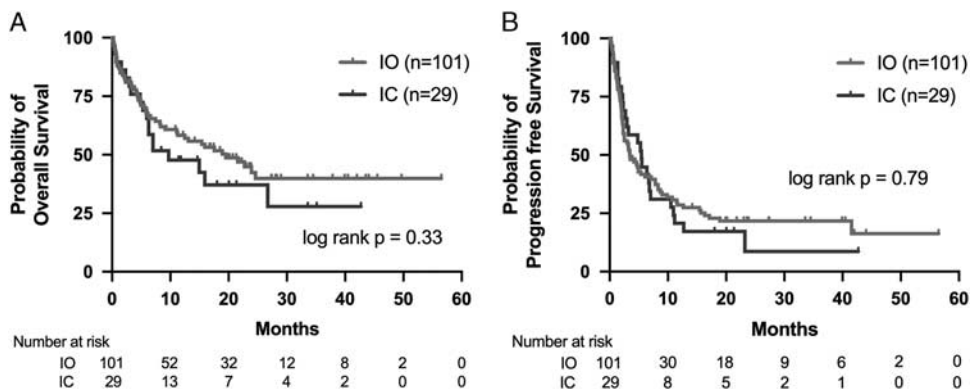
FIGURE 2. Kaplan-Meier curve for overall survival (A) and progression-free survival (B) of patients in the IO or IC groups. IC indicates immunotherapy and chemotherapy; IO, immunotherapy.

However, studies directly comparing ICI monotherapy and ICIs plus chemotherapy in the treatment of naive mUC are still lacking. In this study, we demonstrated that ICIs plus chemotherapy for first-line treatment of cisplatin-ineligible patients did not improve ORR, PFS, or OS compared with ICI monotherapy. Furthermore, we observed that the median OS was significantly longer in the ICI monotherapy group for patients with tumors with high PD-L1 expression.

In Taiwan, atezolizumab and pembrolizumab were approved for cisplatin-ineligible patients with high PD-L1 expression tumors or patients who are ineligible for platinum-based chemotherapy.[10,11] However, uncertainty surrounds whether combining ICIs and chemotherapy for cisplatin-ineligible patients is superior to ICI monotherapy. Health providers and patients face difficulty selecting first-line treatment without scientific data. Combining chemotherapy with ICIs is based on solid evidence from basic research.[18–21] Cytotoxic compounds potentially deplete immunosuppressive regulatory T cells (Treg) and myeloid-derived suppressive cells, shifting the tumor microenvironment toward escaping immune eradication.[22–25] In addition, some chemotherapies induce immunogenic cell death and release damage-associated molecular patterns, leading to the recruitment of antigen-presenting cells (mostly dendritic cells) to the tumor nest and initiating subsequent activation of signals to cytotoxic T cells.[26,27] Although combining ICIs and chemotherapy for lung adenocarcinoma-demonstrated superior

survival benefits to conventional chemotherapy, this therapeutic combination was not as successful in mUC in the pivotal IMvigor-130 or KEYNOTE-361 studies.[12,13,28,29] Furthermore, the IMvigor-130 and KEYNOTE-361 studies did not aim to investigate the efficacy of ICIs plus chemotherapy for patients unfit for cisplatin administration. Therefore, the results of these 2 phase 3 studies cannot be applied to this population.

Our data revealed that the median OS was 19.5 months, and ORR was 34.7% for unselected patients receiving ICI monotherapy. Compared with the OS of 15.9 months and ORR of 23% in the IMvigor-210 Cohort 1 study, patients with mUC in the present study had a higher ORR and longer OS. The reason may be related to a higher proportion of UTUC in our cohort (56.2%) compared with the UTUC proportion in IMvigor-210 (28%) and KEYNOTE-052 (19%). Previous studies had featured a distinctively high incidence and prevalence of UTUC in Taiwan.[30] In our hospital, we reviewed 256 patients with mUC receiving chemotherapy between 1997 and 2014, demonstrating a high proportion of UTUC (57%), which is quite comparable with the current study.[31] It is because the tumorigenesis of UTUC in Taiwan is distinct from that in western countries. UTUC is well known for its association with Lynch syndrome and microsatellite instability. Unlike rare germ line diseases in western countries, the UTUC carcinogenic mechanism had been reported with chronic exposure to aristolochic acid (AA) that induces the TP53
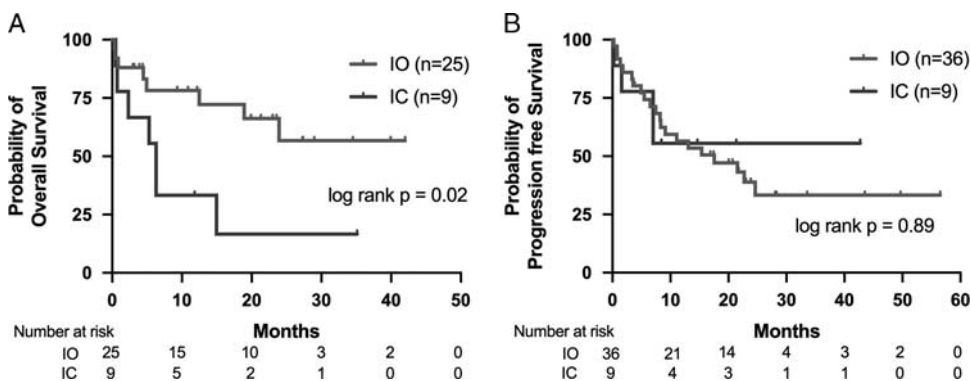
FIGURE 3. Kaplan-Meier estimates of overall survival by IO or IC treatment are shown by high programmed cell death ligand-1 expression (A) and low programmed cell death ligand-1 expression (B). IC indicates immunotherapy and chemotherapy; IO, immunotherapy.
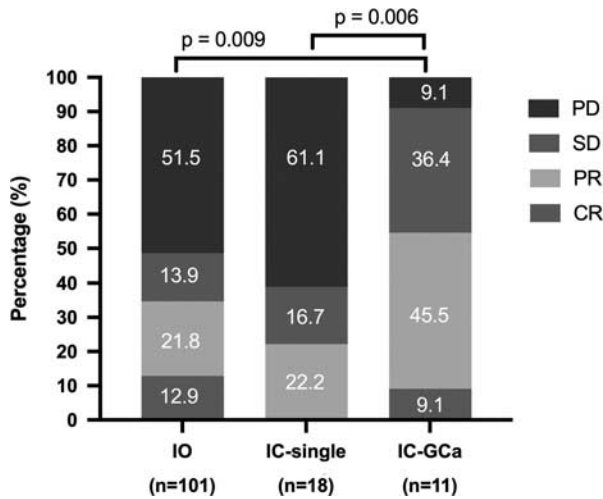
FIGURE 4. Treatment responses of patients in the IO, IC-single, and IC-GCa groups. Log-rank *P* tests for DCR comparison. CR indicates complete response; IC, immunotherapy and chemotherapy; IC-single, immunotherapy plus single-agent chemotherapy; IC-GCa, immunotherapy plus gemcitabine and carboplatin; IO, immunotherapy; PD, progressive disease; PR, partial response.

fingerprint mutation.[32–37] Recent fundamental research has demonstrated that tumors harboring AA mutational signatures are correlated with a higher tumor mutational burden and more predicted tumor-associated neoantigens, implying the potential efficacy of IO in various types of solid tumors.[38–42] By comprehensive whole genomic sequencing analysis of 90 UTUC patients, Lu et al found that UTUC with AA mutational signature had a significantly higher neoantigen burden, increasing tumor-infiltrating lymphocytes and associated with better cancer-specific survival and metastasis-free survival.[38] Further translational research is warranted to determine the genomic characteristics and differences of UTUC, particularly with a focus on AA-associated carcinogenesis and the tumor mutation burden in East Asia.

A small proportion of the patients received carboplatin-based chemotherapy doublet plus IO (n = 11).

The response rate is exceptionally high (54.6%), implying an enhancement of antitumor immunity by platinum-based chemotherapy. A recent study suggested that only cisplatin and gemcitabine doublet, rather than carboplatin and gemcitabine doublet, had such a synergic effect.[43] However, our study did not include patients treated with cisplatin, and further larger real-world study is required to refine the existing evidence.

Because cisplatin-ineligible patients have more comorbidities and are much more fragile, using single-agent chemotherapy with ICIs to enhance immunogenicity and optimally limit treatment-related adverse effects is a reasonable therapeutic option. However, evidence supporting such a combination is still scarce, and more research is urgently needed. Parikh et al[44] reported that the ORR and DCR of pembrolizumab combined with docetaxel or gemcitabine in patients with platinum-refractory mUC were 42% and 58%, respectively. In a phase 1b study evaluating the efficacy and safety of combining avelumab with eribulin mesylate for mUC treatment, 1 patient had a durable partial response (7.8 mo) and the DCR was 66.7%.[45] The efficacy and response rate of combination therapy exceeded those in pivotal trials of ICI monotherapy. Nevertheless, our data revealed that the ORR of ICIs combined with single-agent chemotherapy (22.2%) was lower than that of ICI monotherapy (34.7%) or ICIs with gemcitabine/carboplatin (54.5%). Moreover, the DCR and PFS of ICIs plus single-agent chemotherapy were significantly inferior to those of the other 2 groups, suggesting that this combination strategy may not be advisable for first-line treatment of cisplatin-ineligible patients.

In the last few years, several survival models composed of independent prognostic factors have been developed for the stratification of ICI administration in patients with mUC. Khaki et al[46,47] reported the largest cohort with 357 patients receiving first-line ICI treatment and identified four independent prognostic factors: ECOG PS ≥ 2, albumin <3.5 g/dL, NLR > 5, and presence of liver metastasis. Our retrospective study confirmed that ECOG PS ≥ 2 and liver metastasis were significant prognostic factors for OS. ECOG PS is considered a practical tool for evaluating the functional status of cancer patients. A decline in ECOG PS was associated with more comorbidity and cachexia status, which increased the clearance of ICIs and led to insufficient
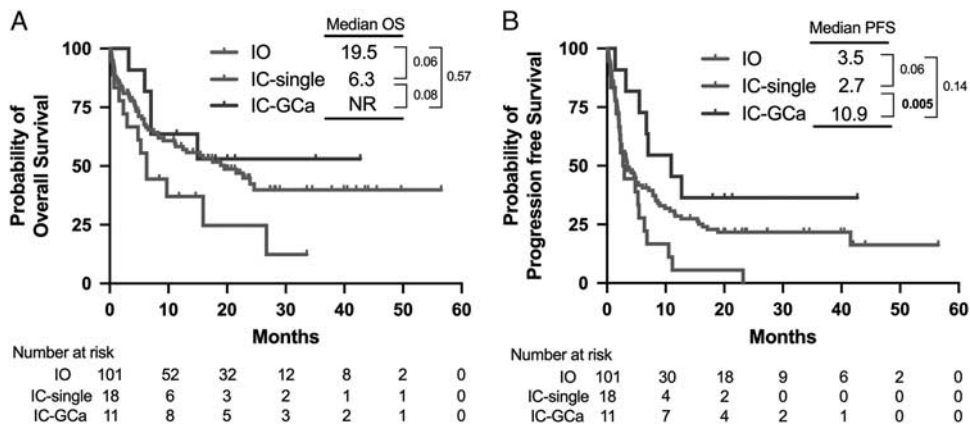
FIGURE 5. OS (A) and PFS (B) of patients in the IO, IC-single, and IC-GCa groups using the Kaplan–Meier method. IC indicates immunotherapy and chemotherapy; IC-single, immunotherapy plus single-agent chemotherapy; IC-GCa, immunotherapy plus gemcitabine and carboplatin; IO, immunotherapy; NR, not reached; OS, overall survival; PFS, progression-free survival.

TABLE 4. Univariate and Multivariate Analysis of Overall Survival

Covariates	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
ECOG ≥2 (vs. 0–1)	3.26 (1.99–5.34)	<0.0001	2.04 (1.18–3.53)	0.01
Liver metastases	2.00 (1.12–3.56)	0.02	2.63 (1.40–4.96)	0.003
Bone metastases	2.14 (1.24–3.67)	0.005	1.59 (0.91–2.79)	0.10
WBC ≥10×10^3/μL (vs. <10)	3.04 (1.84–5.02)	<0.0001	2.39 (1.24–4.63)	0.01
NLR ≥5 (vs. <5)	3.39 (2.05–5.58)	<0.0001	1.70 (0.86–3.36)	0.13
Hb <10 g/dL (vs. ≥10)	2.02 (1.25–3.29)	0.004	1.78 (1.00–3.18)	0.05
Treatment with IO (vs. IC)	1.31 (0.76–2.24)	0.33	0.96 (0.53–1.73)	0.90

ECOG indicates Eastern Cooperative Oncology Group; Hb, hemoglobin; IC, immunotherapy and chemotherapy; IO, immunotherapy; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell count.

drug exposure and a worse OS.[48] Site-specific metastasis, particularly liver metastasis, is considered a critical determinant of ICI responsiveness in mUC.[49] In the KEYNOTE-052 study, the ORR of patients with liver metastasis (n = 11/64, 17%) was significantly lower than that of patients without liver metastases (n = 72/243, 30%). Liver metastases reshape local and systemic immunology by diminishing intratumorally activated CD8 T cells, reducing peripheral T-cell function and diversity, and leading to a systemic immune desert, which can respond poorly to ICI therapy.[50] Several pretreatment peripheral blood parameters, including white blood cell, absolute neutrophil count, absolute lymphocyte count, NLR, Hb, and platelet counts, have been studied to predict ICI response in many solid tumors.[51–53] A comprehensive study by Kobayashi et al[54] combined 4 clinical parameters (PS, liver metastasis, Hb level, and NLR) with building a prognostic model that functioned well in determining the effect on survival. Our results are in line with these findings, demonstrating that the level of Hb (cutoff level, 10 g/dL) and leukocytosis were independent factors for OS. A recent study found that pretreatment reduced Hb was negatively associated with ICI response in patients with non–small cell lung cancer.[55] Notably, baseline Hb level was clinically related to hyperprogressive disease during ICI treatment for patients with hepatocellular carcinoma.[56] Anemia is a common disorder among patients with mUC receiving systemic chemotherapy, and it often represents a clinical marker reflecting the severity of cachexia status.[57,58] The relationship between advanced cancer and anemia is multifactorial. Still, the most critical factors are a high serum level of cytokines, including interleukin-6, tumor necrosis factor-α, and interferon-γ, which reduce erythropoiesis and decrease the response to erythropoietin.[59] In addition, iron-deficiency anemia impairs T-cell proliferation and

function.[60] Recent high-effect research by Zhao and colleagues investigating cancer-related anemia and immunity demonstrated that anemia was associated with declining CD8 T-cell activity through increased immunosuppressive CD45$^+$ erythroid progenitor cells. This effect was found only in patients with cancer and anemia.[61] Our data confirmed the results of this fundamental research. These clinical biomarkers are clinically convenient and cost-effective and could be efficiently utilized in daily practice.

This study has several limitations. First, unlike randomized trials, retrospective studies do not allow the establishment of causative relationships compared with randomized trials. Our goal is to provide real-world experience for clinical reference. Second, the allocation of patients into different treatment groups was based on the physician's choice and patient's preference, leading to inevitable selection bias. On the one hand, patients may be given a type of therapy that does not meet the standard of care, but on the other hand, this study can help with decision-making in day-to-day clinical practice. In addition, the demographic data, including sex, age, ECOG PS, and Bajorin prognostic factors, were not different between the 2 groups. Third, 40% of all patients exhibited unknown PD-L1 values in this study. It is because our study began earlier (April 2016) than the Food and Drug Administration announced a PD-L1 restriction on front-line use of ICI for patients ineligible for cisplatin in June 2018. Furthermore, the distribution of patients whose PD-L1 values were missing was fairly balanced, which minimized potential biases.

Fourth, we did not report the safety profile, especially in the combination group. Finally, our real-world data are based on a small sample size in only 2 medical centers. Although we observed a significant survival benefit in chemotherapy and ICI combination, the clinical application and interpretation of the results should be cautious of its small sample size (N = 12). Further research with a larger sample size may provide better homogeneity and validity.

This study demonstrated that the efficacy of first-line ICI monotherapy and ICIs plus chemotherapy in cisplatin-ineligible patients was similar in ORR, PFS, and OS. For patients with high PD-L1-expression tumors, ICI monotherapy achieved significantly improved survival outcomes compared with ICIs plus chemotherapy. The PFS and OS for ICIs plus single-agent chemotherapy were significantly inferior to those for ICI monotherapy or ICIs plus gemcitabine/carboplatin. Further confirmatory studies are needed to validate our results.

TABLE 5. Subsequent Therapies Post Immune-checkpoint Inhibitors

	IO, n (%)	IC, n (%)	P
Any	18 (17.8)	9 (31)	0.122
Chemotherapy	13 (12.8)	7 (24)	—
Immunotherapy	2 (1.9)	1 (3.4)	—
Others*	3 (2.9)	2 (6.8)	—

*Palliative radiotherapy, FGFR inhibitor, immunotherapy and chemotherapy combination.
IC indicates immunotherapy and chemotherapy; IO, immunotherapy.

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