Patients with advanced or metastatic urothelial carcinoma are generally older and nephroureterectomy is frequently performed in such patients; therefore, cisplatin-based regimen often cannot be applied because of renal insufficiency and poor performance status. Gemcitabine and carboplatin is frequently used as combination chemotherapy for cisplatin-unfit patients and to reduce toxicities. Meanwhile, immune checkpoint inhibitors may be used to reduce toxicities without an efficacy compromise because immune checkpoint inhibitors are available regardless of renal function. The retrospective cohort study conducted by Feld et al. (1) clearly demonstrated inferior short-term but superior long-term survival with first-line immune checkpoint inhibitors relative to carboplatin-based chemotherapy among patients with metastatic urothelial carcinoma treated in routine clinical practice.

Urothelial carcinoma is the sixth most common cancer in the United States, accounting for approximately 3% of cancer-related deaths (2). For advanced or metastatic urothelial carcinoma, platinum-based combination chemotherapy is the standard first-line treatment. In 1992, methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was established as the first standard combination chemotherapy (3). Subsequently, gemcitabine and cisplatin (GC), which showed less adverse events and was as effective as MVAC, was recognized as the new standard combination chemotherapy in 2005 for advanced or metastatic urothelial carcinoma, and currently holds the same position (4).

Unfortunately, after platinum-based chemotherapy, disease progression was frequently observed, and the overall survival (OS) rate at 2 years in patients treated with GC was only approximately 30%; moreover, most patients required a second-line treatment (5). The development of a better treatment strategy has been attempted in the past decade.

Several molecular targeting agents and immune checkpoint inhibitors, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) antibodies, have been tested to establish a standard second-line treatment (6,7). The KEYNOTE-045, phase 3 randomized-controlled trial revealed that the PD-1 antibody pembrolizumab significantly prolonged the OS of patients after platinum-based combination chemotherapy treatment (7). High tolerability and reduced adverse event frequency were noted during PD-1 and PD-L1 antibody treatment (8-11). Patients with advanced or metastatic urothelial carcinoma are generally older and nephroureterectomy is frequently performed in such patients; therefore, cisplatin-based regimen, such as MVAC and GC, often cannot be applied because of renal insufficiency and poor performance status. For such patients, immune checkpoint inhibitors may be used to reduce toxicities without an efficacy compromise because immune checkpoint inhibitors are available regardless of renal function (12,13). Hence, we reviewed multicenter studies reporting the use of immune checkpoint inhibitors as the first-line therapy for patients with advanced or metastatic urothelial cancer who are ineligible...
for cisplatin (12,13).

The KEYNOTE-052 trial with a 5-month median follow-up period revealed that 24% of patients treated with pembrolizumab achieved either a complete or partial response, 23% achieved stable disease, and 62% experienced adverse events with 16% having ≥ grade 3 adverse events. Gemcitabine and carboplatin (GC) is frequently used as combination chemotherapy for cisplatin-unfit patients and to reduce toxicities (14). Compared to carboplatin-based chemotherapy, pembrolizumab tends to be superior for low toxicity and its efficacy in elderly patients (14). In the IMVigor-210 trial (13) that had a long median follow-up period (17.2 months), the objective response rate was 23% and a complete response was achieved in 9% of patients treated with atezolizumab. The median progression-free survival was 2.7 months, median OS was 15.9 months, and 12-month survival rate was 57%. In particular, patients who achieved stable disease had a prolonged median OS of 19.1 months. The OS was considerably longer than the median OS of patients treated with GC (9.3 months) (14). Patients who received atezolizumab and GC revealed a similar median OS of 15.2–15.8 months (5,15). Regarding adverse events, GC was reported to induce severe acute toxicity in 9% of patients characterized by grade 4 thrombocytopenia with bleeding, febrile neutropenia, ≥ grade 3 mucositis causing death, and ≥ grade 3 renal toxicity (14). Adverse events that were ≥ grade 3 were observed in more than half of the patients; neutropenia was the most common at 52.5% (14). Moreover, the most common ≥ grade 3 adverse event observed in patients who received GC was neutropenia (71%), followed by thrombocytopenia (57%) (5). These results suggest that immune checkpoint inhibitors can be safely administered, leading to fewer adverse events than conventional chemotherapy.

In June 2018, the US Food and Drug Administration restricted the use of pembrolizumab and atezolizumab in patients with advanced or metastatic urothelial carcinoma who were unfit for platinum-based chemotherapy and have low PD-L1 expressions (16). The decision was based on the early results of the ongoing phase 3 trial, and it is likely that the conclusion will remain the same. Furthermore, the GC split, wherein the cisplatin dose is split for days 2 and 3 or days 2 and 9, showed better efficacy than GC in cisplatin-unfit patients with advanced or metastatic urothelial carcinoma (17).

Through a single-arm phase 2 study, immune checkpoint inhibitors have been approved; however, few studies have directly compared carboplatin-based chemotherapy to immune checkpoint inhibitors. Using a large sample size of >2,000 patients, Feld et al. evaluated and compared the effectiveness of first-line immune checkpoint inhibitors and carboplatin-based chemotherapy for metastatic urothelial cancer (1). Table 1 shows a summary of open data in studies of first line immune checkpoint inhibitor for metastatic urothelial carcinoma (1,12,13,18,19). The immune checkpoint inhibitor group had a lower survival rate than the carboplatin-based chemotherapy group at 12 months of treatment; however, the immune checkpoint inhibitor group showed a higher survival rate at 36 months, crossing the Kaplan-Meier curves (1). Interestingly, the immune checkpoint inhibitor curve showed a flat long tail at 30% after 24 months. Patients who survived the first 1–2 years of immune checkpoint inhibitor treatment were expected to show long-term survival (1). Although the relationship between PD-L1 expression and response rate of immune checkpoint inhibitors is unclear, patients positive for PD-L1 and treated with immune checkpoint inhibitors have shown the longest survival, whereas those negative for PD-L1 and treated with immune checkpoint inhibitors have the shortest survival. This indicates that the therapeutic effect may be predicted through PD-L1 expression at the time of treatment initiation (1). However, in this real-world study, there may be some limitations. As mentioned, the patient background was unclear; the fact that the site of metastasis or comorbidity was not evaluated may have critically affected patient survival (1). Moreover, Galsky et al. established the definitions of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy: (I) WHO or Eastern Cooperative Oncology Group performance status of 2 or Karnofsky performance status of 60–70%; (II) creatinine clearance (calculated or measured) <1 mL/s; (III) common terminology criteria for adverse events (CTCAE) version 4, grade ≥2 audiometric hearing loss; (IV) CTCAE version 4, grade ≥2 peripheral neuropathy; and (V) New York Heart Association class III heart failure (20); however, there were no clear criteria for cisplatin ineligibility in this study (1). Furthermore, there were some patients who received cisplatin as a second-line treatment; therefore, this result may not be considered as the outcome of immune checkpoint inhibitor treatment for cisplatin-unfit patients (1). This retrospective cohort study had some limitations that require careful attention for better understanding; however, the study clearly demonstrated inferior short-term but superior long-term survival with first-line immune checkpoint inhibitors.
Table 1 The comparison of immune checkpoint inhibitors for urothelial carcinoma

| Variable                      | KEYNOTE-052 (12) | IMVigor-210 (13) | KEYNOTE-361 (18) | IMVigor-130 (19) | Feld et al. (1) |
|-------------------------------|------------------|------------------|------------------|------------------|----------------|
| Type of study                 | Prospective      | Prospective      | Prospective      | Prospective      | Retrospective   |
| Phase of study                | 2                | 2                | 3                | 3                | Retrospective   |
| Status of study               | Complete         | Complete         | Ongoing          | Ongoing          | Complete        |
| ICI                           | Pembrolizumab    | Atezolizumab     | Pembrolizumab    | Atezolizumab     | Nivolumab, pembrolizumab, avelumab |
| Comparison                    | Single arm       | Single arm       | ICI+GC vs. ICI vs. GC | ICI+GC vs. GC | ICI vs. carboplatin-based |
| No. of patients               | 370              | 119              | 990              | 1,200            | 487            |
| Age ≥80 years (%)             | 29               | 21               | N/A              | N/A              | N/A            |
| Gender (%)                    |                  |                  |                  |                  |                |
| Male                          | 77               | 81               | N/A              | N/A              | 74             |
| Female                        | 23               | 19               | N/A              | N/A              | 26             |
| ECOG PS2 (%)                  | 41               | 27               | N/A              | N/A              | 27             |
| Primary location (%)          |                  |                  |                  |                  |                |
| Upper UT                      | 19               | 28               | N/A              | N/A              | 25             |
| Lower UT                      | 81               | 71               | N/A              | N/A              | 75             |
| Median follow up (months)     | 5                | 17.2             | N/A              | N/A              | 7.2            |
| Median PFS (months)           | 2                | 2.7              | N/A              | N/A              | N/A            |
| Median OS (months)            | N/A              | 15.9             | N/A              | N/A              | 9              |
| Response (%)                  |                  |                  |                  |                  |                |
| ORR                           | 24               | 23               | N/A              | N/A              | N/A            |
| Complete response             | 5                | 9                | N/A              | N/A              | N/A            |
| PD-L1 status (%)              |                  |                  |                  |                  |                |
| <1%                           | 17               | 33               | N/A              | N/A              | N/A            |
| ORR                           | 11               | 21               | N/A              | N/A              | N/A            |
| 1–10%                         | 52               | N/A              | N/A              | N/A              | N/A            |
| ORR                           | 20               | N/A              | N/A              | N/A              | N/A            |
| >10%                          | 30               | N/A              | N/A              | N/A              | 22             |
| ORR                           | 39               | N/A              | N/A              | N/A              | N/A            |
| Infiltrating immune cells (%) |                  |                  |                  |                  |                |
| <1%                           | N/A              | 33               | N/A              | N/A              | N/A            |
| ORR                           | N/A              | 21               | N/A              | N/A              | N/A            |
| 1–5%                          | N/A              | 40               | N/A              | N/A              | N/A            |
| ORR                           | N/A              | 21               | N/A              | N/A              | N/A            |
| >5%                           | N/A              | 47               | N/A              | N/A              | N/A            |
| ORR                           | N/A              | 28               | N/A              | N/A              | N/A            |

ICI, immune checkpoint inhibitor; GC, gemcitabine and cisplatin; N/A, not available; ECOG PS, Eastern Cooperative Oncology Group performance status; UT, urinary tract; PFS, progression free survival; OS, overall survival; ORR, overall response rate; PD-L1, programmed death-ligand 1.
relative to carboplatin-based chemotherapy among patients with metastatic urothelial carcinoma treated in routine clinical practice (1). The percentage of PD-L1 expression in tissue may be a promising biomarker of immune checkpoint inhibitors. Moreover, the decision in administration of immune checkpoint inhibitors may require the high percentage of PD-L1 expression (e.g., >10% on the basis of the result of KEYNOTE-052), as already applied in lung cancer clinically on the basis of the result of KEYNOTE-024 (12,21). This study provides important information to facilitate decision-making until the currently pending trial results become available (1).

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau.2020.04.08). 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.

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