Editorial Commentary

# Optimizing frontline therapy in advanced urothelial cancer

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Cisplatin-based combination chemotherapy (CT) has been widely accepted as the initial treatment for cisplatin-eligible patients with metastatic urothelial cancer (mUC) of the bladder and upper urinary tract. Although these tumors are very sensitive to this treatment, only a small proportion of patients with these tumors may be cured, and most of the cases recur eventually within a short time. Another concern associated with this treatment is cisplatin-related toxicity. In addition, not all patients with urothelial cancer are appropriate candidates for cisplatin therapy. Up to 50% of patients with mUC are cisplatin-ineligible patients because of age or comorbidities such as impaired renal function, neuropathy, and heart failure (1). Other CT options for cisplatin-ineligible mUC patients include carboplatin-based combination CT or non-platinum based combination CT (2-4). However, these combinations are inferior due to lower response rates, shorter response durations, and lower OS than cisplatin-based CT (5).

The emergence of immunotherapy (IO) has revolutionized the paradigm of treatment of advanced and mUC. Checkpoint inhibitors target programmed cell death protein 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1) and have shown durable response in approximately 20% of patients with platinum-refractory mUC (6-10). Based on these results, the FDA has approved five PD-1/PD-L1 inhibitors in this setting. In addition, recently, atezolizumab and pembrolizumab have been tested in single-arm trials in cisplatin-ineligible patients with mUC with durable response in ~25% of the study participants (11,12). Based on these, the FDA approved atezolizumab and pembrolizumab as the first-line treatment for cisplatin-ineligible patients with mUC and high expression of PD-L1. However, this approval is primarily based on surrogate endpoints such as objective response rates and not overall survival (OS) data. Furthermore, since there is no direct comparison between CT and IO in this setting, clinicians must adequately manage both therapies at their discretion. In the absence of randomized clinical trials, the most useful data for this population are the indirect comparison between first-line carboplatin-based CT and immune checkpoint blockade therapy in cisplatin-ineligible mUC patients, although the inclusion criteria in these studies were different. This comparison showed that the objective response rate of carboplatin and gemcitabine (42%) (13) was nearly double compared to that of IO such as checkpoint inhibitors (23–24%) (12,14). However, interestingly, the OS rate was 15.9 months and 9.3 months for the atezolizumab and CT study, respectively (15).

New retrospective real-world data by Feld *et al.* (16) demonstrate the effects of carboplatin-based CT and systemic IO as a primary treatment for those patients with locally advanced or mUC who are ineligible for cisplatin-based CT. In this study, using the Flatiron Health database, the data of patients receiving primary carboplatin-based CT

(n=1,530) or PD-1/PD-L1 inhibitor (n=487) were analyzed. Propensity score-based analysis was used to reduce the risk of selection bias inherent in the retrospective nature of the study. The main finding was that the group treated with IO had a lower OS at 12 months (39.6% versus 46.1%) but a higher OS at 36 months (28.3% *vs.* 13.3%) than did the group receiving carboplatin-based CT. This is probably due to the nature of the response observed with IO. Indeed, patients who do not respond to IO and reported hyperprogression less frequently than in reality might account for early reduced survival in the IO group. In contrast, the long-term benefits of IO include providing a durable response to a significant proportion of patients. This result is similar to the data on the durability of the reaction by conventional PD-1/PD-L1 inhibitors (7,9-12,15,17).

The study by Feld *et al.* (16) has several limitations including the lack of available data on key prognostic variables used to determine cisplatin ineligibility of enrolled patients such as renal dysfunction, performance status, presence of visceral metastasis, hearing loss, peripheral neuropathy, and heart failure. Furthermore, these real-world data might not reflect the real-world situation because, after May 18, 2018, monotherapy using immune checkpoint inhibitors is used to treat cisplatin-ineligible mUC patients who are PD-L1 positive (approximately 30% of all tumor) or those who are ineligible for any platinum-containing CT. Lastly, there was a difference in the rate of receiving second-line therapy between the carboplatin-based CT and systemic IO groups (47% versus 22%) which may affect the OS, the primary endpoint of the study. Second-line regimen using cisplatin-based CT was used in 10 (9.4%) and 37 (5.7%) patients who might be cisplatin-eligible. Despite the above limitations, the results of this study provide the clinicians awaiting phase III trials with important findings to advise those patients with mUC in the first-line setting who are ineligible for cisplatin-based CT.

The high initial response rate of carboplatin-based CT in cisplatin-ineligible mUC patients as the first-line treatment makes it an important treatment option for patients with high tumor burden that induces pain and local obstruction Moreover, IO drugs are the first second-line treatment available after progression of the disease following first-line CT. Further clinical trials and long-term follow-up are needed to define the role of IO drugs in the treatment of locally advanced and mUC in a first-line setting. Currently, four large randomized phase III trials are underway to help understand the efficacy and toxicity of IO drug monotherapy and platinum-based CT with IO drug combinations (18-21). However, in the absence of subsequent randomized trials, the study by Feld *et al.* (16) is quite considerable. In addition, some subgroups of patients (possibly suffering from high tumor burden) may still benefit from CT suggesting that IO drugs could be a promising option in this setting. However, according to the findings of the improved 12-month OS with carboplatin-based CT but superior 3-year OS with IO, we need a precise IO strategy including the development of predictive markers for determining the first-line CT in cisplatin-ineligible mUC patients.

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## Footnote

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure from (available at http://dx.doi.org/10.21037/tau.2020.04.03). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that the accuracy or integrity of the work has been appropriately investigated and resolved.



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