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Editorial

Crucial crossroads: Making the right choice for first-line therapy in advanced urothelial cancer

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Over the past decade, there have been significant changes in the treatment landscape for metastatic urothelial cancer. The initial decision regarding cisplatin eligibility remains pivotal, with the majority of patients being ineligible due to factors such as performance status or renal function. Typically, patients undergo 4–6 cycles of initial chemotherapy (gemcitabine/cisplatin [GEM/CIS] or GEM/carboplatin), with a historical median progression-free survival (PFS) of around four months on cessation.[1]

Given the limited uptake of second-line therapy, the importance of selecting the optimal first-line treatment cannot be overstated. Notably, maintenance avelumab has shown promising results, demonstrating a 31% reduction in the risk of death compared to placebo, making it a potential standard of care alongside chemotherapy followed by maintenance avelumab. Overall survival (OS) was prolonged with avelumab despite 72.0% of patients in the control arm receiving subsequent anticancer drug therapy, including PD-1/PD-L1 inhibitors (53.1%). In real-world clinical practice, only 30–40% of patients are able to receive second-line therapy. The long-term results confirm the long-term safety profile of avelumab 1L maintenance, with 19.5% of patients receiving ≥2 years of treatment and a low overall rate of discontinuation due to treatment related adverse effects (TRAEs) (10.2%).[2]

The Checkmate 901 trial investigated GEM/CIS plus nivolumab specifically for cisplatin-eligible patients, with positive outcomes observed. Out of 608 randomized patients, both OS and PFS showed improvement, with a noteworthy complete response rate of approximately 22%.[3] Particularly impressive was the extended median duration of complete response, exceeding three years.

This regimen entails up to six cycles of cisplatin/gemcitabine followed by nivolumab until disease progression or toxicity, with a maximum duration of 2 years. Unlike other regimens, such as Enfortumab Vedotin (EV) pembrolizumab, which continue until toxicity or progression, this approach offers patients a better quality of life post-chemotherapy cessation. Although EV pembrolizumab represents significant progress, its association with neuropathy-related interruptions underscores the importance of considering alternative options. Furthermore, EV is not yet available in many countries, and the EV Pembrolizumab regimen is definitely much more costly than the other two treatment options, limiting its widespread application in low-middle-income countries.[4]

Given the remarkable complete response rates and enhanced quality of life with gem-cis-nivo, it may warrant consideration, especially in patients with lymph node-only disease, a subgroup known to exhibit higher complete response rates to cisplatin-based chemotherapy. Biomarkers like ERCC2 could potentially aid in patient selection, as seen in the neoadjuvant setting, although further

validation in metastatic disease is warranted. Despite the efficacy of EV pembrolizumab, the gem-cis-nivo regimen could still find utility, especially considering its cost-effectiveness and finite duration.

EV is Food and Drug Administration (FDA)-approved for patients with platinum- and immune checkpoint inhibitor–refractory advanced urothelial carcinoma, but its confirmatory trials did not include patients whose disease had progressed after maintenance avelumab. A retrospective analysis of registry data showed that patients who received platinum-based chemotherapy and maintenance avelumab followed by EV had higher objective response rates but overall similar PFS and OS to patients in the trial that led to its FDA approval.[5]

The problem with the Checkmate 901 is that on looking at both PFS and OS curves for the first 4–5 months (that corresponds to the duration of the first six cycles of chemo plus IO), there is absolutely no difference with both the curves are absolutely hugging each other. This points toward the previous observation that the approach of sequential chemotherapy followed by maintenance immunotherapy is the way forward in advanced urothelial cancers. In addition, this study included only patients who were cisplatin-eligible, which makes it difficult to adopt in around 50% of the advanced urothelial cancer patients who are actually cisplatin-ineligible.

After looking at all the above options, choosing wisely remains the key, and the final decision should be based on the patient's choice besides financial and therapeutic toxicities of the various treatment options.

REFERENCES

1. Kaur J, Singh A, Shah M, Chandrani P, Chougule A, Kapoor A, *et al*. Erdafitinib for tumors with FGFR3 mutation: A promising targeted therapy. Cancer Res Stat Treat 2023;6:288-95.
2. Powles T, Park SH, Caserta C, Valderrama BP, Gurney H, Ullén A, *et al*. Avelumab first-line maintenance for advanced urothelial carcinoma: Results from the JAVELIN bladder 100 trial after ≥2 years of follow-up. J Clin Oncol 2023;41:3486-92.
3. Van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, *et al*. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. N Engl J Med 2023;389:1778-89.
4. Kaushik MR, Kapoor A, Singh HP, Suresh P, Mulajkar D, Rathore A, *et al*. Real world experience on patterns of usage and toxicity profile of immunotherapy drugs in Indian patients: A prospective observational study. Med J Armed Forces India 2023. Doi: 10.1016/j.mjafi.2023.07.007
5. Nizam A, Jindal T, Jiang CY, Alhalabi O, Bakaloudi DR, Talukder R, *et al*. Outcomes in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin (EV) after switch maintenance avelumab (MAv) in the UNITE study. J Clin Oncol 2024;42(suppl 4):abstr537.

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