Treatment of Cisplatin/Platinum-Ineligible Metastatic Urothelial Carcinoma

Subjects: Oncology

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Metastatic urothelial cancer (mUC) is an aggressive malignancy with limited treatment options. Cisplatin-based chemotherapy has been the standard of care in metastatic urothelial cancer (mUC). However, many patients with comorbidities cannot receive cisplatin or its alternative, carboplatin. 'Cisplatin-ineligible' and 'platinum-ineligible' patients lacked effective therapy options. However, the combination of enfortumab vedotin (EV), an antibody–drug conjugate targeting Nectin-4, with pembrolizumab (P), an antibody targeting the programmed death-1 (PD-1) immune checkpoint, is changing the status quo of frontline mUC treatment, with potential synergy seen in the EV-103 and EV-302 clinical trials.

Keywords: cisplatin ineligibility ; platinum ineligibility ; metastatic urothelial cancer (mUC) ; treatment ; standard of care

1. Definition of Cisplatin Ineligibility

Patients with treatment-naïve mUC can be classified into three categories: cisplatin eligible, cisplatin ineligible but carboplatin eligible, and platinum ineligible (cisplatin and carboplatin ineligible). Up to half of patients with mUC meet one common criterion for cisplatin ineligibility [1]. In one of the widest efforts to define cisplatin ineligibility in mUC, Galsky et al. (2011) proposed a working group definition of cisplatin-ineligible mUC, the criteria for which can be found in **Table 1** [2]. The presence of one criterion out of five is enough to establish ineligibility.

Table 1. Comparison of the consensus criteria for ineligibility for cisplatin- and platinum-containing regimens in mUC. Abbreviations: ECOG PS: European Cooperative Oncology Group performance status; KPS: Karnofsky Performance Scale; CrCl: creatinine clearance; NYHA: New York Heart Association; dB: decibels.

Parameters	Cisplatin Ineligibility (Galsky et al., 2011) [2]	Platinum Ineligibility (Gupta et al., 2022) [3]
ECOG PS	≥2, or KPS of ≤60%–70%	≥3
CrCl	<60 mL/min	<30 mL/min
NYHA Heart Failure Class	≥3	>3
Peripheral neuropathy	Grade ≥ 2 (i.e., sensory alteration or paresthesia, including tingling, but not interfering with activities of daily living)	Grade ≥ 2
Different parameters	Hearing loss (measured at audiometry) of 25 dB at 2 contiguous frequencies	ECOG PS of 2 and CrCl < 30 mL/min

A possible exception may occur if a patient's sole criterion for ineligibility is borderline renal function (creatinine clearance of 40–60 mL/min) [4]. In that case, one notable strategy is a dose split of cisplatin with short duration and enhanced hydration, which has demonstrated increased nephroprotective effects and possibly similar efficacy in prospective studies with no comparator arms [5][6].

2. Definition of Platinum Ineligibility

Platinum ineligibility automatically entails ineligibility for both cisplatin and carboplatin. In clinical practice, carboplatin ineligibility is often determined using physicians' common sense, mainly based on an assessment of overall performance status and renal function. Many oncologists would prefer not to prescribe carboplatin to frail elderly patients with limited physiological reserves [4] and frequent comorbidities, such as worsening heart disease and uncontrolled diabetes mellitus (DM).

The lack of a formal definition of carboplatin ineligibility led to the first initiative by Gupta et al. (2019) to survey genitourinary oncologists about their experiences and choices [7]. The need for a formal definition became more urgent when the FDA restricted the use of pembrolizumab and atezolizumab to cisplatin-ineligible patients with tumors with high expression of programmed death ligand 1 (PD-L1) or platinum-ineligible patients regardless of PD-L1 status, despite the fact that both treatments had previously been approved unconditionally for 1L treatment of cisplatin-ineligible patients [8].

In November 2022, the FDA approval of atezolizumab for 1L mUC was completely withdrawn, and pembrolizumab was restricted to 1L treatment of platinum-ineligible patients [9]. Thus, Gupta et al. (2022) surveyed 60 genitourinary medical oncologists in the United States and created an updated consensus definition of platinum ineligibility for mUC patients meeting at least one of five criteria, as shown in **Table 1** [3]. The same group estimated a prevalence of <10% carboplatin ineligibility among LA/mUC patients [3].

3. Treatment of Cisplatin-Ineligible Metastatic Urothelial Carcinoma

3.1. Previous Standard of Care

The ancillary role of cisplatin-based chemotherapy in LA/mUC was established more than three decades ago with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), yielding a median OS (mOS) of 13 months compared to single-agent cisplatin [10]. Later, dose-dense (or accelerated) MVAC became an accepted option in clinical practice given its more favorable toxicity profile in the phase 3 EORTC 30924 trial, despite sharing a similar OS with standard MVAC [11]. However, gemcitabine plus cisplatin (GC), another frequent SOC treatment for LA/mUC, also showed response rates and survival outcomes similar to those of MVAC, with the exception of better tolerability and less toxicity in favor of GC [12].

In cisplatin-ineligible patients, gemcitabine plus carboplatin (GCa) was the 1L alternative to GC, based on the results of the historical trial EORTC 30986 [13]. Although GCa yielded a response rate of ~40%, the OS (usually ~9 months) was shorter than that of GC (15–16 months). After achieving stable disease with 4–6 cycles of platinum-based regimens, the landmark phase 3 JAVELIN Bladder-100 trial, in which 40% of enrolled patients received GCa, found significant OS benefit with avelumab as maintenance therapy regardless of PD-L1 status [14]. JAVELIN Bladder-100 was the first trial in more than 3 decades to prove the amelioration of survival outcomes for patients without disease progression, including stable disease, on 1L platinum-based chemotherapy. An OS benefit was attributed to avelumab compared to best supportive care (21.4 mo vs. 14.3 mo; Hazard Ratio (HR) = 0.69, 95% CI 0.56–0.86, p = 0.001). Despite the expected lower response rate with GCa, subgroup analyses of JAVELIN Bladder-100 consolidated the survival benefit of avelumab regardless of receipt of GC or GCa [15]. However, the research did not report the rate of primary progression on GCa prior to randomization, which would be anticipated to be higher than that of GC.

Other less frequently used regimens in the chemotherapy era replaced cisplatin with taxanes, such as paclitaxel or docetaxel, or even adopted single-agent chemotherapy (gemcitabine) [16][17]. However, no phase 3 trial involving these non-platinum-based regimens or sequential treatment doublets was performed in the population of interest.

3.2. The New Standard of Care

Enfortumab vedotin (EV) is a breakthrough humanized monoclonal ADC targeting Nectin-4, a highly expressed protein in urothelial cancer [18]. It induces an anti-proliferative and pro-apoptotic effect on cancer cells through the release of monomethyl auristatin E (MMAE), a tubulin-toxic chemotherapeutic agent [18]. After being internalized into the cell to release MMAE [19], EV exhibits targeted cytotoxicity while minimizing systemic toxicity.

Cohort K of the phase 2 study EV-103/KEYNOTE-869 randomized treatment-naïve and cisplatin-ineligible patients to receive EV, either alone or in combination with pembrolizumab (EVP). In the latest updates from this cohort, the combination arm achieved an objective response rate (ORR) of 64.5% and a complete response rate (CRR) of 10.5%, with a median duration of response (mDOR) not yet reached, compared to an ORR of 45.2% and mDOR of 13.2 months in the EV monotherapy group [20][21].

Despite no formal statistical comparison between the survival outcomes of the EV vs. EVP arms, the high, durable, and early-onset responses to EVP were unprecedented in the chemotherapy era. Interestingly, the overwhelming majority of patients enrolled in Cohort K had visceral disease, a negative prognostic factor and a Bajorin risk factor [22]. The percantage of patients with ECOG PS 2 was also balanced between treatment arms in this cohort with heavy metastatic burden. In subsequent analysis of Cohort K, EVP activity was consistently seen in subgroups with worse prognosis, especially patients with visceral metastases (ORR in EVP arm: 65.6% [52.7–77.1]) [21].

Additionally, a 4-year follow up of EV-103 dose escalation (Cohort A) consolidated the deep (ORR 73.1%, CRR 15.6%) and durable (mDOR: 22.1 months; mOS: 26.1 months) responses to EVP [23]. The safety profile in this follow-up was consistent with previous reports. While the 2019 and 2021 FDA approvals of EV concerned platinum- or immunotherapy-exposed patients [24], the latest accelerated approval in April 2023 covered treatment-naïve, cisplatin-ineligible patients [25].

More recently, phase 3 EV-302 confirmed the survival endpoints achieved with EVP vs. platinum-based chemotherapy (GC or GCa) [26]. EVP almost doubled the mOS (31.5 mo vs. 16.1 mo; HR 0.47; 95% CI: 0.38–0.58, $p < 0.00001$) and median PFS (mPFS) (12.5 mo vs. 6.3 mo; HR 0.45, 95% CI: 0.38–0.54, $p < 0.00001$) at a median follow-up of 17.2 months. The response rate achieved by EVP was also significantly higher (67.7% vs. 44.4%, $p < 0.00001$). Together, these findings have propelled EVP toward a “dethroning” of the stagnant SOC of chemotherapy.

The preference for using EVP over chemotherapy will likely be dictated by the interaction of the regimen’s toxicity profile with the patient’s medical comorbidities. Currently, there are no contraindications to EV in its official prescribing information. However, warnings and precautions have been issued for patients with preexisting DM and previous peripheral neuropathy [27]. Beyond these previously reported treatment-related adverse events (TRAEs), no additional safety signals for EV or pembrolizumab were reported in these trials.

4. Treatment of Platinum-Ineligible Metastatic Urothelial Carcinoma

4.1. Previous Standard of Care

With the stagnant absence of any agent shown to have better efficacy than cisplatin- and carboplatin-based regimens, platinum-ineligible LA/mUC patients had an unmet therapeutic need for more than two decades. The most compelling indication for pembrolizumab in this population comes from phase 2 KEYNOTE-052 [28]. Even after a median follow-up of almost 5 years, 1L pembrolizumab conferred lasting clinical response, with an ORR of 28.9%, which was even higher for patients with CPS ≥ 10%. Median OS was 11.3 months and the 12- and 24-month OS rates were 46.9% and 31.2%, respectively [28]. Based on these results, the FDA granted approval for pembrolizumab as 1L treatment for treatment-naïve, platinum-ineligible patients with mUC [8].

Atezolizumab was previously granted accelerated FDA approval, based on results from phase 2 Imvigor210 in cisplatin-ineligible patients [29]. Later, the results of Phase 3 Imvigor130 and KEYNOTE-361, comparing chemotherapy to ICI monotherapy, showed that atezolizumab lacks clinical benefit in cisplatin-eligible patients with low or negative PD-L1 expression [30]. Thus, atezolizumab was limited to cisplatin-ineligible patients with PD-L1+ tumors (≥5% expression in immune cells) and platinum-ineligible patients regardless of PD-L1 expression [6][8]. The combination of atezolizumab and either GC or GCa also failed to meet a co-primary endpoint of OS benefit in phase 3 Imvigor 130 and only showed a PFS benefit [30]. After withdrawal of the indication of atezolizumab by the manufacturing company, approval was withdrawn in the US for platinum-ineligible patients regardless of PD-L1 status [9].

4.2. The New Standard of Care

As discussed earlier, the superior outcomes of EVP compared with platinum-based chemotherapy, regardless of fitness to receive platinum compounds, support the use of this combination for 1L treatment of platinum-ineligible patients [26].

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