Editorial Commentary

Balancing effectiveness, toxicity, and individualization: enfortumab vedotin in advanced urothelial cancer

Nuowei Wang, Karl H. Tully

Department of Urology and Neurourology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany

Correspondence to: Karl H. Tully, MD. Department of Urology and Neurourology, Marien Hospital Herne, Ruhr-University Bochum, Hölkeskampring 40, 44625 Herne, Germany. Email: karl.tully@elisabethgruppe.de.

Comment on: Rosenberg JE, Mamtani R, Sonpavde GP, *et al*. Health-related Quality of Life in Patients with Previously Treated Advanced Urothelial Carcinoma from EV-301: A Phase 3 Trial of Enfortumab Vedotin Versus Chemotherapy. Eur Urol 2024;85:574-85.

Keywords: Bladder cancer; metastatic disease; antibody-drug conjugate (ADC); quality of life; adverse events

Submitted Dec 20, 2024. Accepted for publication Mar 17, 2025. Published online Mar 26, 2025.
doi: 10.21037/tau-2024-743
View this article at: https://dx.doi.org/10.21037/tau-2024-743

The EV-301 Phase 3 trial compared enfortumab vedotin (EV) to standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma (mUC) previously treated with platinum-based chemotherapy and programmed cell death protein-1 and programmed cell death ligand 1 (PD-1/L1) inhibitors. The current sub-study by Rosenberg et al. evaluates the patient-reported outcomes (PRO) related to health-related quality of life (HRQoL) using tools like the European Organisation for Research and Treatment of Cancer C30 Quality of Life questionnaire (EORTC QLQ C30) (1).

The trial shows that patients receiving EV obtained an overall better HRQoL than those treated with third- or later-line salvage chemotherapies (SCTs).

More patients in the EV arm confirmed clinically meaningful improvement for all functioning scales (fatigue, pain, dyspnea, and constipation), with odds ratios (ORs) ranging from 1.67 to 2.76. The most remarkable difference was in pain reduction, with patients in the EV arm having 2.76 times higher odds of significantly reducing pain than those in the chemotherapy arm.

Also, patients in the EV group experienced deterioration of HRQoL later than patients undergoing SCT, although deterioration for appetite loss occurred earlier with EV.

The results support EV's benefits in symptom management and HRQoL for advanced urothelial carcinoma, complementing its survival and safety data.

As an open-label trial, EV-301 was affected by declining but similar compliance rates in both groups. Additionally, decreasing completion rates due to disease progression or death may bias results in favor of responders, a common challenge in oncology trials. PROs are essential for understanding the patient's experience during treatment but must be interpreted cautiously due to biases, missing data, and subjectivity (2). The authors mention the influence of treatment awareness as the trial was open-label. Patients were aware of their treatment assignment and may report better or worse outcomes based on expectation rather than actual effects.

The findings emphasize the importance of prolonging survival and maintaining quality of life during therapy without curative intent. This is a critical consideration in oncology, especially for patients with advanced and incurable diseases.

Nevertheless, the toxicity profile of EV is unique due to its mechanism of action (3). The most common toxicities include fatigue, peripheral neuropathy, and cutaneous toxicities. In particular, cutaneous toxicity can severely impact HRQoL and may often be underestimated in clinical practice. In the EV-301 trial, 47% of EV patients had all-grade treatment-related skin reactions. Grade 3 or higher skin reactions occurred in 14.5% of patients receiving EV compared to 0.7% in the chemotherapy group. Skin reactions that resulted in dose interruption occurred in 11%, and 8% required dose reductions. Skin reactions led to treatment withdrawal in 4% of the patients (4).

The cutaneous toxicities include rash, pruritus, exanthema, and, in severe cases, even Stevens-Johnsons

Table 1 Current and future landscape of antibody-drug conjugates in urothelial carcinoma

	Enfortumab vedotin	Sacituzimab govetican	Datopotamab deruxtecan	Disitamab vedotin	Trastuzumab deruxtecan
Target	Nectin-4	Trop-2	Trop-2	HER2	HER2
FDA approval	Approved for locally advanced and mUC	Withdrawal from Gilead 10/24	Not yet approved for UC	Not yet approved for UC	Not yet approved for UC
Key side effects	Rash, peripheral neuropathy, fatigue, hyperglycemia	Neutropenia, anemia, diarrhea, nausea, fatigue	Nausea, stomatitis, alopecia, interstitial lung disease	Neuropathy, leukopenia, elevated liver-enzymes, alopecia	Interstitial lung disease, nausea, anemia, diarrhea
Main trials	EV-301, EV-103	TROPHY-U-01, TROPiCS-04	TROPION-PanTumor01	RC48-C005, RC48-C009	DESTINY-PanTumor02

FDA, Food and Drug Agency; mUC, metastatic urothelial carcinoma; UC, urothelial carcinoma.

syndrome and toxic epidermal necrolysis, both potentially life-threatening adverse events (3,5).

Routine skin assessments starting with EV therapy should be performed since skin-related adverse events typically occur within the first few treatment cycles. Frequent and thorough follow-up and early involvement of dermatology are essential, as fatal cases have been documented in clinical trials and post-marketing reports (3,6).

Furthermore, EV can lead to hyperglycemia, which occurs more frequently in patients with baseline hyperglycemia or obesity [body mass index (BMI) $\geq$30 kg/m^2] (4). As a frequently occurring comorbidity, these patients need strict monitoring of their blood sugar levels. Moreover, extreme cases of poorly controlled diabetes mellitus may be one of the few absolute contraindications of EV in daily clinical practice.

The relevance of EV itself will continue to change over the next few years. With the implementation of new drugs for advanced urothelial carcinoma, such as other antibody-drug conjugates (ADCs) like datopotamab-deruxtecan or other targeted approaches like FGFR3 inhibition using erdafinitib, patients and clinicians alike will encounter a wide variety of different but particular toxicity profiles, which may impact HRQoL to various degrees (*Table 1*) (3,7).

The general mode of action of ADCs is based on three pillars: (I) the target-directed antibody; (II) the cytotoxic payload; and (III) the linker connecting the first two. The individual combination of these three parts may lead to three different forms of drug delivery and their consequent effects. First, on-target (meaning at the intended antigen relating to the specific antibody)/on-site (relating to the desired location, i.e., the cancer cell itself). This describes the intended effect of targeted drug delivery to the tumor itself. Second, on-target/off-site payload delivery, which results in target-specific toxicities. For EV, this is based on NECTIN-4-induced endocytosis in a non-cancerous NECTIN-4 positive cutaneous cell, releasing the cytotoxic payload in healthy tissue (8-10). Third, off-target/off-site payload delivery. As in most monomethyl auristatin E (MMAE)-based ADCs, this form of payload delivery of EV most likely derives from uncontrolled disconnection between the antibody, the cleavable linker, and the cytotoxic payload, resulting in free payload in the systemic circulation resulting in adverse events such as peripheral neuropathy, anemia, neutropenia, and hepatic toxicity (3,11,12). The last form of unintended payload delivery can also be seen in other ADCs, such as sacituzumab govitecan, and is mainly associated with the respective linker used for each ADC (3,13). Patients randomized into the control arm of the current EV-301 study, on the other hand, underwent undirected chemotherapy using docetaxel, paclitaxel, or vinflunine. These drugs are not only undirected, meaning they are bound to cause off-site side effects, but are usually associated with some side effects, in which EV could outperform these therapies (1). In particular, fatigue and constipation are among these therapies' most common side effects (4). Comparing different ADCs with these SCT options may thus look vastly different based on the antibody, linker, and payload, respectively.

As EV is a NECTIN-4-directed ADC, it is reasonable that this drug may be associated with favorable outcomes in patients showing a high expression of NECTIN-4, resulting in a higher proportion of the payload being delivered to the target. While the initial trials examining EV in previously treated urothelial cancer seemed to show a nearly ubiquitous expression of NECTIN-4, a current analysis by Klümper *et al.* found a decreasing or even absent NECTIN-4 expression in heavily pretreated mUC (14). Moreover,

an earlier study by Challita-Eid *et al.* found that 17% of their cohort with mUC were NECTIN-4 negative (10). Thus, patients showing a lower degree of NECTIN-4 expression may not reap the same on-target benefits as patients with a high degree of NECTIN-4 expression. Still, they may face the same potential off-target and off-site side effects of this ADC. This, in turn, may further negatively impact a patient's HRQoL.

As a result, pretherapeutic evaluation of potential targets using immunohistochemical staining or next-generation sequencing may help find the best therapeutic option for each patient, leading to a more tailored approach to cancer therapy. It should thus be an essential cornerstone in today's patient-centered, personalized tumor therapy, leading us away from the current "one-size-fits-all" standard of care. While this approach may result in EV not always being the best option for all patients, as the current pivotal trials seem to suggest, it may help achieve the most crucial goal in cancer therapy: to achieve optimal oncologic outcomes and maintain a high level of HRQoL—regardless of the medication used.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-2024-743/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-2024-743/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Rosenberg JE, Mamtani R, Sonpavde GP, et al. Health-related Quality of Life in Patients with Previously Treated Advanced Urothelial Carcinoma from EV-301: A Phase 3 Trial of Enfortumab Vedotin Versus Chemotherapy. Eur Urol 2024;85:574-85.
2. Churruca K, Pomare C, Ellis LA, et al. Patient-reported outcome measures (PROMs): A review of generic and condition-specific measures and a discussion of trends and issues. Health Expect 2021;24:1015-24.
3. Reike MJ, Bahlburg H, Brehmer M, et al. Side effects of drug-antibody conjugates enfortumab-vedotin and sacituzumab-govitecan in targeted therapy in cancer. Cancer Epidemiol 2024;90:102574.
4. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021;384:1125-35.
5. Yang H, Yu X, An Z. Cutaneous Toxicity Associated With Enfortumab Vedotin: A Real-Word Study Leveraging U.S. Food and Drug Administration Adverse Event Reporting System. Front Oncol 2021;11:801199.
6. Lacouture ME, Patel AB, Rosenberg JE, et al. Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin. Oncologist 2022;27:e223-32.
7. Siefker-Radtke AO, Matsubara N, Park SH, et al. Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select FGFR alterations: cohort 2 of the randomized phase III THOR trial. Ann Oncol 2024;35:107-17.
8. Murata M, Ito T, Tanaka Y, et al. NECTIN4 Expression in Extramammary Paget's Disease: Implication of a New Therapeutic Target. Int J Mol Sci 2020;21:5891.
9. Brancati F, Fortugno P, Bottillo I, et al. Mutations in PVRL4, encoding cell adhesion molecule nectin-4, cause ectodermal dysplasia-syndactyly syndrome. Am J Hum Genet 2010;87:265-73.
10. Challita-Eid PM, Satpayev D, Yang P, et al. Enfortumab

Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. Cancer Res 2016;76:3003-13.
11. Rosenberg J, Sridhar SS, Zhang J, et al. EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4-Positive Solid Tumors, Including Metastatic Urothelial Carcinoma. J Clin Oncol 2020;38:1041-9.
12. Nguyen TD, Bordeau BM, Balthasar JP. Mechanisms of ADC Toxicity and Strategies to Increase ADC Tolerability. Cancers (Basel) 2023;15:713.
13. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol 2021;39:2474-85.
14. Klümper N, Ralser DJ, Ellinger J, et al. Membranous NECTIN-4 Expression Frequently Decreases during Metastatic Spread of Urothelial Carcinoma and Is Associated with Enfortumab Vedotin Resistance. Clin Cancer Res 2023;29:1496-505.

Cite this article as: Wang N, Tully KH. Balancing effectiveness, toxicity, and individualization: enfortumab vedotin in advanced urothelial cancer. Transl Androl Urol 2025;14(3):503-506. doi: 10.21037/tau-2024-743