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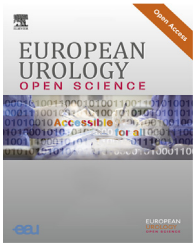

European Association of Urology

Brief Correspondence

Enfortumab Vedotin–related Cutaneous Toxicity and Radiographic Response in Patients with Urothelial Cancer: A Single-center Experience and Review of the Literature

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Abstract

Enfortumab vedotin (EV) is an antibody-drug conjugate approved for the treatment of refractory advanced urothelial cancer. Cutaneous toxicity is well described but has not been correlated with response. In this retrospective single-center study, data from patients treated with more than one dose of EV between December 2017 and June 2022 were analyzed. Of 56 patients with a median age of 69 yr, 41 (73.2%) were male and 27 (48.2%) had any-grade skin toxicity. For all 51 patients evaluable by physician-assessed Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the response rate was 41.2%. For those with cutaneous toxicity, the response rate was 57.7%; for those without cutaneous toxicity, it was 24.0% (p = 0.0145). All three patients with complete response experienced cutaneous toxicity, and two of these responses remain durable 5 and 24 mo off EV. The median starting weight and body mass index (BMI) were, respectively, 80.86 kg and 26.53 kg/m^2 among patients with cutaneous toxicity, and 69.37 kg and 23.29 kg/m^2 in patients without (p = 0.0129 and 0.0014, respectively). In this small dataset, EV-related cutaneous toxicity was more common in patients with higher weight and BMI at baseline, and was associated with disease response. Confirmation in prospective trials may confirm this association and lead to an important clinical biomarker of response.

Patient summary: We evaluated patients with urothelial cancer who were treated at our institution with enfortumab vedotin (EV). We found that patients who experienced the common side effect of any type of skin toxicity, such as rash or itching, were more likely to have improvement in their cancer from EV treatment than those who did not experience skin toxicity. Patients with higher weight and body mass index when starting EV tended to have more skin toxicity. We conclude that presence of skin toxicity might help doctors make decisions about how to manage the care of patients with EV in the future.

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Enfortumab vedotin (EV) is an antibody-drug conjugate, with an anti–nectin-4 monoclonal antibody linked to the chemotherapeutic monomethyl auristatin E (MMAE) [1,2]. EV is approved in the USA and Europe for patients with locally advanced or metastatic urothelial cancer with disease progression following chemotherapy and a PD-1/L1 inhibitor, with a response rate of 44% [3]. In patients with advanced urothelial cancer who were ineligible for cisplatin and had previously been treated with a PD-1/L1 inhibitor, the response rate was similar at 52% [4].

Enfortumab 1.25 mg/kg is administered intravenously on days 1, 8, and 15 of a 28-d cycle, capped at 125 mg per dose. Toxicities include blood glucose elevation, neuropathy, fatigue, and gastrointestinal and cutaneous toxicity [3,5–8]. Cutaneous adverse events include various rash and pruritus, and rare potentially life-threatening or fatal manifestations such as Stevens-Johnson syndrome. Cutaneous toxicity typically presents in early cycles, and low-grade events can be managed with supportive care such as antihistamines, topical steroids, and moisturizers. Grade $\geq$3 events necessitate dose interruption, pulse oral steroid, and consideration of dermatology consultation. Rechallenge when appropriate can be considered with dose reduction for grade $\leq$3 events that resolve to grade $\leq$1; discontinuation is recommended for grade 4. An outstanding review on the management of EV cutaneous toxicity has been published [9]. Several case reports describe grade 3–5 cutaneous toxicity, but few include cancer outcomes in these cases. An EV-related cutaneous toxicity literature review is presented in the Supplementary material.

With Johns Hopkins Institutional Review Board approval, a retrospective review of EV-treated patients was performed to evaluate whether cutaneous toxicity correlated with a response. Cutaneous toxicity was defined as any-grade new skin rash or pruritus (Supplementary material). Radiographic response was determined by physician-assessed Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patient characteristics were summarized using descriptive statistics, and compared between patients with and without EV-related cutaneous toxicity using Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. Risk difference along with 95% confidence interval (CI) on disease response rate, disease control rate, complete response (CR), partial response (PR), stable disease (SD), mixed response, disease progression (PD), and progression-free survival (PFS) between two groups were assessed using the chi-square test. A mixed response was defined as tumor shrinkage and progression on imaging in different locations in patients continuing treatment for clinical benefit. Kaplan-Meier curves and median survival times with 95% CI for PFS between the two groups were assessed by the log-rank test. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Two-tailed p values were considered statistically significant at $p < 0.05$.

From December 2017 until May 2022, 68 patients were identified through the Johns Hopkins infusion pharmacy database. Seven treated on EV combination trials were excluded, leaving 61 who received single agent enfortumab. Three patients received C1D1 only, and quickly clinically declined or expired from disease progression, and two who transferred care and were lost to follow-up were not included in this dataset. Fifteen (26.8%) female and 41 (73.2%) male patients received more than one dose of single agent EV with clinical follow-up and were eligible for toxicity review. Fifty-one patients had radiographic follow-up and are included for an efficacy review (CONSORT flow diagram in Supplementary Fig. 1).

The mean age was 70.1 yr (95% CI 34–90), with 84% treated in the $\geq$3 line; the majority had Eastern Cooperative Oncology Group performance status (PS) 0 or 1. Twenty-seven (48%) patients developed any-grade cutaneous toxicity, which occurred in early cycles (mean 1.3 cycles, range 1–4): 16 developed grade 1, seven developed grade 2, two each developed grade 3 and grade 4 skin toxicity, and three required hospitalization due to severe cutaneous and other toxicities.

Patient characteristics are presented in Table 1 and Supplementary Figure 2. Fifteen (44.1%) out of 34 bladder cancer patients and ten (50.0%) out of 20 upper tract urothelial carcinoma patients developed cutaneous toxicity. Those with cutaneous toxicity had significantly higher baseline weight (84.0 vs 71.7 kg, $p = 0.0129$) and body mass index (BMI; 26.5 vs 22.3 kg/m^2, $p = 0.0014$). Drug allergy history was reviewed, with no difference in cutaneous toxicity between those with or without known drug allergies.

Of 56 patients, 51 had radiographic follow-up and are included for efficacy review. The response rate (RR; RR = CR + PR) for the full cohort was 41.2% and the disease control rate (= CR + PR + SD) was 68.7%. The best physician-assessed RECIST response for each group is presented in Table 2. The response rate was 57.7% for those with cutaneous toxicity and 24.0% for those without it ($p = 0.0145$). All three (100%) patients who had CRs developed rash. Four patients experienced Grade $\geq$3 skin toxicity, which occurred within the first two cycles. Three patients had a PR noted soon after skin toxicity. One remains now in CR for 24+ months and another with a PR recently noted, and both off anticancer therapy. One had an early PR but died from complications after prolonged hospitalization for toxicity. One patient with no further imaging after recovery from skin toxicity chose supportive care alone, now off therapy for 12+ mo but not evaluable for response.

Of the eight African-American patients treated with EV, six (75%) were treated with a full dose in cycle 1 and all the six patients developed EV-related skin toxicity. Outcomes for these six patients were as follows: three (50.0%) PRs, one (16.7%) SD, and one (16.7%) PD. The two African-American patients who did not experience cutaneous toxicity were frail and therefore had prophylactic dose reduction from cycle 1 (1 mg/kg) at physician discretion. Their best response was SD and PD. Highlighted case narratives from our cohort are presented in the Supplementary material. The median PFS was 6.0 mo (95% CI 4.0–8.0) for all patients with cutaneous toxicity and 4.5 mo (95% CI 4.0–8.0) for patients without ($p = 0.24$; Supplementary Fig. 3). Neuropathy occurred in later cycles than skin toxicity, and there was a nonsignificant trend that correlated with response. We suspect that patients who have a clinical benefit from EV

Table 1 – Characteristics of toxicity-evaluable patients with and without EV-related cutaneous toxicity (*n* = 56)

Characteristic	Pts without cutaneous toxicity (*N* = 29)	Pts with cutaneous toxicity (*N* = 27)	*p* value [a]
Sex, *n* (%)			0.4568
Female	9 (31.0)	6 (22.2)	
Male	20 (69.0)	21 (77.8)	
Race, *n* (%)			0.1390
White or Caucasian	23 (79.3)	20 (74.1)	
African American	2 (6.9)	6 (22.2)	
Asian	3 (10.3)	–	
Hispanic or Latino	1 (3.4)	1 (3.7)	
Estimated GFR, median (IQR) [b]	53.0 (38.0–65.0)	53.0 (41.0–61.0)	0.9216
Cancer primary location, *n* (%)			0.3677
Bladder	19 (65.5)	15 (55.6)	
UTUC	10 (34.5)	10 (37.0)	
Bladder and UTUC	–	2 (7.4)	
Metastatic sites, *n* (%)			0.4401
Lymph nodes only	6 (20.7)	8 (29.6)	
Visceral disease	23 (79.3)	19 (70.4)	
Liver	13 (44.8)	10 (37.0)	0.5538
Lungs	10 (34.5)	12 (44.4)	0.4456
Bones	4 (13.8)	4 (14.8)	1.0000
BMI on C1D1 (kg/m^2), median (IQR)	22.3 (19.9–25.6)	26.5 (25.0–28.1)	0.0014
Weight on C1D1 (kg), median (IQR)	71.7 (57.9–77.4)	84.0 (70.6–88.9)	0.0129
Number of EV cycles, median (IQR)	3.0 (2.0–5.0)	5.0 (2.0–7.0)	0.0742
Line of therapy, *n* (%)			0.8709
2	5 (17.2)	4 (14.8)	
3	16 (55.2)	17 (63.0)	
≥4	8 (27.6)	6 (22.2)	
ECOG PS on C1D1, *n* (%)			0.0013
0	3 (10.3)	14 (51.9)	
1	23 (79.3)	10 (37.0)	
2	3 (10.3)	3 (11.1)	
Neuropathy development/progression, *n* (%)	6 (20.7)	14 (51.9)	0.0150
Cycle of neuropathy development/progression (*N* = 20), median (IQR)	2.5 (2.0–4.0)	3.0 (2.0–4.0)	0.4995

BMI = body mass index; C1D1 = cycle 1 day 1; ECOG PS = Eastern Cooperative Oncology Group performance status; EV = enfortumab vedotin; GFR = glomerular filtration rate; IQR = interquartile range; Pts = patients; UTUC = upper tract urothelial carcinoma.

[a] The *p* value is based on Wilcoxon rank sum test for continuous variable and Fisher exact test for categorical variable.

[b] CKD-EPI or MDRN Eqn ml/min/1.73 m^2—patients on hemodialysis at EV initiation included.

therapy continue treatment longer and therefore are at a higher risk of neuropathy (Supplementary material).

To our knowledge, this is the first report demonstrating an association between EV-related cutaneous toxicity and response. Cutaneous toxicity appeared to correlate with increased weight and BMI at baseline, indicating a possible dose-related relationship. In our small dataset, all African-American patients who received more than one full EV dose developed cutaneous toxicity. We do not believe that this observation could be explained by obesity in this population, as the baseline weight (range 46.6–93.1 kg, median 69.2, mean 61.7) and BMI (range 18.21–28.1, median 23.6, mean 23.6) were reflective of the entire cohort. This observation could reflect increased susceptibility of African-American patients to EV-related cutaneous toxicity by an undescribed mechanism.

The pathophysiology of EV-related cutaneous adverse events is not completely understood, although nectin-4 is expressed in normal skin, and thus an on-target effect is postulated [2]. Brentuximab vedotin (BV), another antibody-drug conjugate that is approved for lymphomas, also carries an MMAE payload linked to an anti-CD30 antibody [4]. In 611 patients treated over a decade with BV, rash was the most common adverse event and correlated with a higher frequency and dosing of BV, indicating that the MMAE payload dose likely contributes to cutaneous toxicity [10]. Given that two of four patients with the highest-grade toxicity were treated at maximum capped doses, we hypothesize that the degree of drug exposure is driving both toxicity and response at least in part. Cutaneous toxicity occurred in the first cycle in many, and was higher in PS 0 patients, likely reflective of patients receiving full dosing of enfortumab in cycle 1. Furthermore, dose reduction is a mitigation strategy for skin and other toxicities, further supporting a drug exposure to EV as a driver of side effects. Neuropathy occurred in later cycles than skin toxicity and was not correlated with response, but was higher in those with skin toxicity, perhaps reflective of a longer treatment duration in those responders with skin toxicity (Supplementary Table 2). Criticisms of this report include physician-reported response assessment, retrospective analysis, single center, and small sample size. Furthermore, the small sample size could not allow for multivariable analyses, and thus we could not account for potential confounding factors. Confirmation in larger retrospective and prospective trials, as well as with pK values, may confirm this clinical association and hypothesis, and lead to an important clinical biomarker of response. It also highlights the importance of early recognition and maximal supportive care of cutaneous toxicity.

***Author contributions*:** Jean Hoffman-Censits had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hoffman-Censits, Hahn, McConkey, Vlachou.
Acquisition of data: Vlachou, Hoffman-Censits, Matoso.
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Table 2 – Disease response, control, and progression rates [a] in response-evaluable patients with and without cutaneous toxicity (*n* = 51)

	N (%)			
	Pts without cutaneous toxicity (*N* = 25)	Pts with cutaneous toxicity (*N* = 26)	Risk difference (95% CI) (toxicity vs nontoxicity)	*p* value
Disease response	6 (24.0)	15 (57.7)	33.7% (5.6%–57.9%)	0.0145
CR	–	3 (11.5)	11.5% (–3.9% to 30.6%)	0.2353
PR	6 (24.0)	12 (46.2)	22.2% (–4.9% to 47.0%)	0.0979
Disease control	16 (64.0)	19 (73.1)	9.1% (–17.1% to 34.9%)	0.4849
SD	10 (40.0)	4 (15.4)	–24.6% (–48.4% to 0.8%)	0.0644
MR	–	3 (11.5)	11.5% (–3.9% to 30.6%)	0.2353
PD	9 (36.0)	4 (15.4)	–20.6% (–44.9% to 4.0%)	0.1164

CI = confidence interval; CR = complete response; MR = mixed response; PD = disease progression; PR = partial response; Pts = patients; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UTUC = upper tract urothelial carcinoma.
[a] Based on best physician-determined RECIST response.

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Appendix A. Supplementary data

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