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RESEARCH LETTER

Effect of Enfortumab Vedotin Dose Adjustment on Efficacy in Metastatic Urothelial Carcinoma: A Retrospective Single-Center Experience

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Introduction

Cancer of the urinary tract (bladder, ureter, renal pelvis, and urethra) is the 6th most common cancer in the United States, with urothelial carcinoma (UC) being the most common histologic subtype, accounting for 90%.[1] Enfortumab vedotin (EV) was approved via accelerated approval in December 2019 followed by full approval in July 2021 for use in patients with locally advanced or metastatic urothelial carcinoma (mUC) who had previously received a programmed death-1/programmed death ligand-1 (PD-1/PD-L1) immune checkpoint inhibitor (ICI) and platinum containing chemotherapy or, if cisplatin-ineligible, received at least one prior line of therapy.[2,3] EV is an antibody drug conjugate that binds to the cell adhesion protein, nectin-4, on the surface of tumor cells and intracellularly releases monomethyl auristatin E (MMAE), a cytotoxic agent that disrupts microtubules and causes cell cycle arrest.[4]

In the pivotal Phase III trial, EV-301, EV compared to single agent chemotherapy (docetaxel, paclitaxel, or vinflunine) in patients with mUC previously treated with platinum chemotherapy and an ICI showed significantly improved overall survival (OS), progression free survival (PFS), and overall response rate (ORR). However, the incidence of treatment related adverse events (TRAEs) was high (51%) at the starting dose of 1.25mg/kg D1, D8, and D15 of a 28-day cycle. TRAEs were managed with stepwise 0.25 mg/kg dose reductions.[2,5] Koshkin et al assessed EV in patient populations excluded from the EV-301 trial and noted similar efficacy and a comparable discontinuation rate of 15% for TRAEs; however, dose reductions and interruptions were not described in detail.[6]

Anecdotal experience and an internal quality medication use evaluation at our institution found that EV dose reductions and adjustments are frequent in clinical practice, motivating the current study to further investigate the impact of EV dose changes on clinical cancer-related outcomes. To our knowledge, no study has assessed the impact of EV dose reduction and/or interruption on efficacy. Given the high frequency of dose-limiting adverse events with EV, the objective of this study was to assess the impact of dose holds and adjustment captured by relative dose intensity on cancer-related outcomes.

Materials and Methods

A single-center retrospective study was completed at The James Cancer Hospital at The Ohio State University (OSU; Columbus, OH) including patients with a diagnosis of mUC who received at least one dose of monotherapy EV between December 1, 2019 and August 31, 2022. Protected populations (<18 years old, inmates, and pregnant patients) and patients receiving EV for a clinical trial were excluded. The study was approved by the OSU Institutional Review Board

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(Protocol #2022C0175). Informed consent was waived by the IRB as this retrospective study was considered minimal risk. The study complies with the Declaration of Helsinki.

Demographic, disease, and treatment information was abstracted from the electronic medical record. Relative dose intensity (RDI) was calculated as the ratio of delivered dose during the time on EV to the standard full dose during the same length of time in days.[5,7] Due to the estimated small cohort of patients who never received a dose reduction, we chose to use RDI instead of comparing any dose reduction versus no dose reduction. For statistical comparison, patient cohorts were defined as receiving either >80% or ≤80% RDI. The cutoff of 80% was chosen, in part, because it captures the difference between one versus numerous dose reduction steps. For example, decreasing the dose 20% over 90 days is equivalent to an RDI of 80%, but decreasing by two steps per package insert, ie, 40% dose reduction, over 90 days is equivalent to an RDI of 60%. As the calculation was day sensitive, it was also able to capture differences in schedule changes. For example, removing day 15 and changing to day 1 and day 8 of a 21-day cycle over 90 days would result in an RDI of 90%; if a patient was delayed two weeks for an illness during that 90 day period and missed a dose, their RDI would be reflective of that.

The primary outcome was PFS, defined as months from first dose of EV to clinical or radiographic progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death, censored at date of last follow-up. Secondary outcomes included ORR [rate of complete response (CR) or partial response (PR) at best response by RECIST v1.1], OS (months from first dose of EV to death, censored at date of last follow-up), proportion of patients who discontinued EV by reason for discontinuation, and incidence and type of adverse drug reactions resulting in dose reduction.

Demographic and clinical data were summarized with descriptive statistics, including medians, ranges, and frequencies. Continuous variables were compared with a two-sample *t*-test or a Wilcoxon Log rank test depending on the distribution of each variable. Discrete variables were compared using Fisher's Exact test. The Kaplan-Meier method with Log rank test was used to compare PFS and OS between patient cohorts. Association between covariates and both PFS and OS was assessed using univariate Cox proportional hazards models. Covariates that were significantly different between cohorts were included in multivariable Cox proportional hazards models. All analyses were conducted using SAS version 9.4.

Results

Fifty-three patients met inclusion criteria, of which 45.3% (n=24) had an RDI >80% and 54.7% (n=29) had an RDI ≤80%. Demographics and clinical characteristics are summarized in Table 1. Median duration of treatment was 70 days and 20.8% (n=11) of patients had >3 prior regimens for mUC. All characteristics were similar between RDI groups except median weight and serum creatinine, which were both significantly higher in the RDI ≤80% cohort (p=0.001 and p=0.022, respectively).

Median follow-up until death or censoring for OS was 5.9 months. Dose reductions occurred in 71.7% (n=38/53) of patients; 24.5% (n=13/53) had an empiric dose-reduction starting on cycle 1, day 1 based on discretion of the treating physician. Doses were reduced 63.2% (n=24/38) of the time by percentage changes (ex. 1.25 mg/kg to 1.0 mg/kg) and 36.8% (n=14/38) via schedule changes (ex. Changing to day 1, day 8 of a 21-day cycle). Both percentage and schedule changes occurred in 29.0% (n=11/38) of dose reduced patients. EV was discontinued in 86.8% (n=46) of patients by the time of data cutoff. No patients discontinued EV due to treatment intolerance. Thirty-four patients (34/53 = 64.2%) discontinued therapy due to progression (including death). Three patients transitioned care to an outside institution and were censored at last follow-up. Nine patients were censored when an off-label agent was added to EV. Seven patients remained on monotherapy EV at data cutoff.

As shown in Figure 1A, PFS was not significantly different between RDI cohorts; median PFS was 5.1 months in RDI>80% vs 3.8 months in RDI≤80% (log-rank p=0.904; univariate Cox proportional hazards model: hazards ratio (HR) 1.039, 95% CI [0.559–1.929], p=0.904). Despite adjusting for body weight and serum creatinine (the two variables that were significantly different between cohorts) there continued to be no significant difference in PFS between RDI cohorts (multivariable Cox proportional hazards model: HR 0.802, 95% CI [0.374–1.722], p=0.572).

OS was not significantly different between RDI cohorts, as shown in Figure 1B. Median OS was 13.7 months in RDI>80% vs 10.2 months in RDI≤80% (log-rank p=0.174; univariate Cox proportional hazards model: HR 0.616, 95%

Table 1 Demographics and Clinical Characteristics

Characteristic	Overall Cohort (n=53)	RDI ≤80% (n=29)	RDI >80% (n=24)	P-value
Median age (years)	67 [52–84]	68 [52–84]	67 [54–80]	0.667
Male sex	33 (62.3)	21 (72.4)	12 (50)	0.500
Serum creatinine (mg/dL)	1.19 [0.6–2.7]	1.3 [0.6–2.7]	1.0 [0.6–1.8]	0.022
Weight (kg)	79.9 [54.7–110.4]	87.0 [56.6–110]	72.6 [54.7–100]	0.001
ALT (U/L)	16 [4–162]	17 [4–162]	14 [7–88]	0.401
AST (U/L)	18 [7–180]	20 [7–88]	17 [10–180]	0.325
Total bilirubin (mg/dL)	0.4 [0.2–7.2]	0.5 [02.-7.2]	0.4 [0.2–2.6]	0.305
History of diabetes	11 (20.8)	8 (27.6)	3 (12.5)	0.308
CKD	28 (52.8)	18 (62.1)	10 (41.7)	0.173
Stage >4	1 (1.9)	0 (0)	1 (10.0)	
ECOG Performance Status				0.186
>2	12 (22.6)	9 (31.0)	3 (12.5)	
Number of prior regimens				0.234
0	3 (5.7)	2 (6.9)	1 (4.2)	
1	21 (39.6)	12 (41.4)	9 (37.5)	
2	18 (34.0)	9 (31.0)	9 (37.5)	
>3	11 (20.8)	6 (20.7)	5 (20.8)	
Prior cisplatin for mUC	19 (35.8)	10 (34.5)	9 (37.5)	1.000
Upper tract (ureter or renal pelvis)	22 (41.5)	11 (37.9)	11 (45.8)	0.588
FGFR2 or FGFR3 alteration	6 (11.3)	4 (13.8)	2 (8.3)	0.259

Note: Values given in median [range], number (%).
Abbreviations: RDI, relative dose intensity; ALT, alanine transaminase; AST, aspartate aminotransferase; CKD, chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; mUC, metastatic urothelial carcinoma; FGFR, fibroblast growth factor receptor.

CI [0.305–1.246], p=0.178). Adjusting for body weight and serum creatinine, difference in OS between cohorts remained insignificant (multivariable Cox proportional hazards model: HR 0.584, 95% CI [0.247–1.382], p=0.221).

The ORR was not significantly different between RDI groups (45.83% for RDI>80% vs 44.83% for RDI≤80%, p=0.999). The only complete responses (n=2) were seen in the RDI ≤80% group, and neither had progressed at data collection cutoff.

In a further analysis, we evaluated if the method of dose reduction, either by percentage or schedule change, was associated with PFS or OS. The subset of patients that received a dose reduction by schedule change (n=14), had no difference in PFS (univariate HR 0.564, 95% CI [0.293–1.086], p=0.463) or OS (univariate HR 0.54, 95% CI [0.264–1.106], p=0.818) between the RDI>80% and RDI≤80% cohorts. Among the subset of patients that received a dose reduction by percentage change (n=24), had no difference in PFS (univariate HR 0.744, 95% CI [0.278–1.993], p=0.556), between the RDI>80% and RDI≤80% cohorts. However, this subset of patients did have a significant difference in OS (univariate HR 0.254, 95% CI [0.07–0.919], p=0.038) favoring the RDI>80% cohort.

Treatment related adverse events (TRAEs) resulted in dose modification in 64.2% (n=34) of patients. Of these TRAEs resulting in dose modification, most common were maculopapular rash (12.8% of all patients), infection (10.9%), fatigue

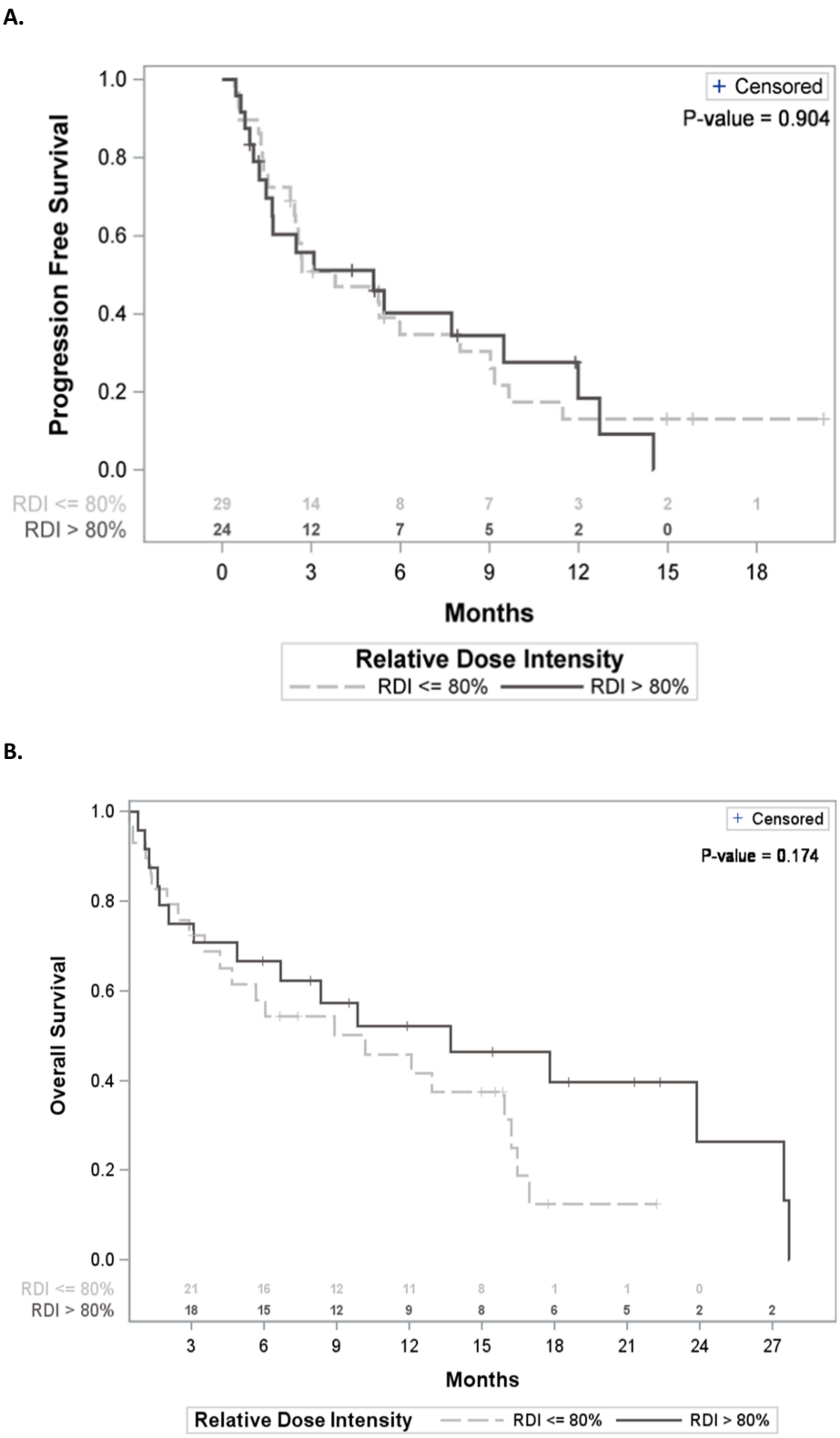

Figure 1 Progression-free survival (PFS) and overall survival (OS) by dose-intensity. PFS (**A**) and OS (**B**) between RDI >80% (solid line) and ≤80% (dashed line) groups.

(6.4%), transaminitis (6.4%), and peripheral neuropathy (5.8%). Hematologic TRAEs resulting in dose modifications were less common (neutropenia 4.5%, anemia 0.6%, thrombocytopenia 0.6%).

Discussion

We performed a retrospective study to determine the impact of dose reduction of EV on efficacy. EV dose reductions were frequent but reductions equaling >80% versus ≤80% RDI did not significantly impact mUC clinical outcomes. PFS, OS, and ORR were similar between cohorts of patients who received RDI>80% and RDI≤80%, and were also similar to those reported in the EV-301 trial.[2,4] The prevalence of dose reductions in our study, 71.7%, was higher than the 32.4% reported in the EV-301 trial, likely due to inclusion of a more heavily pre-treated patient population with worse performance status than those enrolled in the trial.[2] Although patients in our study received lower RDI than those in the EV-301 trial, cancer-related outcomes remained similar even in a difficult to treat population. The incidence of TRAEs leading to dose reduction was higher in our study than in EV-301; but the distribution of grade 3 and 4 TRAEs mirrored the dose-limiting adverse events found in the trial.[2] Overall the lack of negative impact on efficacy of dose reduction, along with improved tolerability, supports the day 1 and 8 dosing of EV on a 21-day cycle that recently received accelerated approval in combination with pembrolizumab in patients with mUC who are ineligible for cisplatin. In real world practice, further dose reduction may be necessary and, based on our study, is not expected to negatively impact outcomes. However, given the small size of our retrospective study, larger prospective studies are needed to validate these results.

Limitations to our study include the retrospective nature and small sample size. Due to the nature of retrospective chart review studies, the toxicity data are only as complete and accurate as the documentation in the electronic medical record and there is potential for selection bias. Validation and further investigation in larger prospective cohorts of patients are warranted. Evidence-based dose modification of EV will be increasingly important to the field as EV is being investigated in earlier metastatic disease settings and in the peri-operative setting for localized urothelial carcinoma.

Conclusion

This study increases confidence that dose reducing EV, an agent with a high incidence of TRAEs, >80% versus ≤80% RDI does not significantly negatively impact efficacy in patients with mUC. Larger studies with pharmacokinetic and pharmacodynamic analyses are warranted.

Abbreviations

mUC, metastatic urothelial carcinoma; EV, enfortumab vedotin; PFS, progression free survival; OS, overall survival; ORR, overall response rate; TRAEs, treatment related adverse events.

Data Sharing Statement

Data may be available on request to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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