Original paper

First experience in treating advanced urothelial cancer with enfortumab vedotin. Single-centre retrospective study of patients qualified for a rescue access procedure

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Introduction: Urothelial carcinoma is the most common type of urinary tract malignancy. Current treatment options, including platinum-based chemotherapy or immunotherapy, present significant challenges, ranging from limited efficacy to severe toxicities. Recent developments in antibody-drug conjugates (ADC), such as enfortumab vedotin (EV), promise to significantly improve overall survival. The study aims to evaluate the efficacy and tolerability of EV. In addition, we highlight the observed benefits of next-line treatment after progression.

Material and methods: This retrospective study involved 16 patients with advanced urothelial cancer treated with EV at the Department of Genitourinary Oncology, Maria Skłodowska-Curie National Research Institute of Oncology between November 2022 and November 2023. The study evaluated patients' medical history, response to EV treatment, and side effects. Notably, the study included patients who had already exhausted standard treatment options and who were treated with EV through a rescue access procedure.

Results: Partial response was observed in 4 out of 9 (44%) patients with available imaging. Common terminology criteria for adverse events (AE) grade 3 and 4 were observed in 3 out of 16 patients, which subsequently required dose reduction.

Conclusions: Enfortumab vedotin demonstrates effectiveness in real-world settings in treating advanced urothelial cancer. Proper management of AE in experienced centres may further prolong survival. Personalized treatment and the development of new ADC represent the future for improved patient outcomes.

Key words: advanced urothelial cancer, enfortumab vedotin (EV), antibody-drug conjugates (ADC), toxicity.

Contemp Oncol (Pozn) 2023; 27 (4): 224–229
DOI: https://doi.org/10.5114/wo.2023.134751

Introduction

Urothelial carcinoma (UC) is the most common primary malignancy of the urinary tract [1]. While the bladder is by far its most common site, it can also be found in the upper urinary tract – in the renal pelvis or ureters upper tract UC is a relatively rare malignancy, accounting for 5–10% of all UC cases [2]. Smoking and occupational exposures, such as dye and rubber manufacture, are significant risk factors [3, 4]. Obesity and socioeconomic disparities are also linked to increased bladder cancer incidence. Genetic factors such as GST and NAT2 gene variants, as well as somatic mutations, contribute to disease development [5]. Genetic alterations in *FGFR2* or *FGFR3* play a crucial role in erdafitinib therapy, which showed a confirmed objective response rate (ORR) of 40% [6]. Urothelial carcinoma primarily affects older individuals, with a median diagnosis age of 72 years for men and 75 years for women [7]. Approximately 25% of urothelial bladder cancer cases are muscle invasive, often requiring systemic treatment and linked to poor long-term outcomes [4, 8]. Urothelial carcinoma presenting at an advanced stage poses significant challenges due to limited treatment options.

Nevertheless, systemic treatment of metastatic UC is currently undergoing a rapid evolution. Platinum-based chemotherapy is considered the best first-line therapy for all patients fit to receive either cisplatin or carboplatin. If disease control is achieved, maintenance immunotherapy with avelumab should be initiated. In the case of failure of first-line chemotherapy treatment the next recommended line of treatment consists of an anti-PD-1/PD-L1 agent [9–11]. Importantly, it should be emphasized that whatever treatment regimen is chosen, it should always be tailored to the patient's clinical condition and tumour overgrowth.

Chemotherapy is widely used in many cancers, and in the past, it was the backbone of treatment for almost all cancers [12]. However, this form of systemic treatment is associated with low specificity, frequent and serious toxicities, and dosing difficulties [12, 13]. The constantly increasing number of mutations in cancer cells is responsible for acquired resistance to treatment, which may eventually develop regardless of the type of treatment

used – starting from classical chemotherapy and ending with kinases inhibitors or immunotherapy. Therefore, in modern oncology, it is necessary to develop appropriate treatment sequences and constantly search for new, more effective drugs such as enfortumab vedotin (EV). Clinical trials have shown that EV significantly prolonged survival compared to standard chemotherapy in patients with locally advanced or metastatic UC who had previously received platinum-based treatment and a PD-1 or PD-L1 inhibitor [14, 15].

Enfortumab vedotin is an antibody-drug conjugate (ADC) composed of a fully human monoclonal antibody specific for nectin-4 and monomethyl auristatin E (MMAE) [16, 17]. The drug molecule binds to nectin-4 and then is endocytosed into the cell and intracellularly releases MMAE, which disrupts microtubule formation. Necitn-4 is a cell-adhesion molecule that is highly prevalent in UC and may contribute to tumour cell growth and proliferation [16, 17]. These properties make it possible to influence precisely and effectively a tumour's growth by disrupting its mitotic divisions.

Enfortumab vedotin is administered intravenously on days 1, 8, and 15 of a 28-day cycle. The most common toxic effects include fatigue, skin toxicity, neuropathy, and blood glucose elevation. [15] Cutaneous toxicity usually occurs as an early adverse event, and it is crucial to quickly and effectively prevent the toxicity from intensifying. To this end, dose reduction may be necessary if symptomatic treatment, such as antihistamines, topical steroids, moisturizers, or pulse corticosteroid therapy, does not help.

The aim of our study was to assess the effectiveness and treatment tolerance of EV in the real-world setting in patients who have utilized all available therapeutic options. This study is also meant to emphasize the need for early diagnosis of side effects, and their proper control can prolong survival. Furthermore, we highlight the need for follow-up lines after EV treatment failure.

Material and methods

Patient collection

This retrospective analysis included 16 patients with advanced urothelial cancer treated with EV in the Maria Skłodowska-Curie National Research Institute of Oncology from 14th November 2022 to 25th November 2023. To our knowledge, it is the first place in Poland in which patients were able to receive EV. We included all patients who started receiving EV between 14th November 2022 and 9th November 2023. The initial dosing of EV was 1.25 mg/kg for all patients. Dose modifications were based on the Summary of Product Characteristics. Each patient had a complete blood count evaluated before starting the course of treatment with EV, and laboratory results were evaluated regularly during therapy to detect any potential side effects early on. This study was performed in line with the principles of the Declaration of Helsinki.

Data collection

The database contained detailed information on age, gender, clinicopathological factors, laboratory results, comorbidities, medications, adverse events, sites of metastases, Eastern Cooperative Oncology Group (ECOG) performance score, and outcome data associated with individual patients. Laboratory tests were carried out by the Diagnostic Department of the National Research Institute of Oncology using a Sysmex XN-1000. Counts of inflammatory cells for calculating immune inflammation biomarkers (neutrophil-lymphocyte ratio – NLR, platelet-lymphocyte ratio – PLR) were taken from laboratory results, which were done immediately prior to treatment initiation. Emerging adverse events (AE) were assessed in accordance with the common terminology criteria for adverse events (CTCAE) v5.0 [18]. Clinical data were extracted from medical records, and mortality data were obtained from the Polish national database. Detailed characteristics of the study group at the start of the study are shown in Table 1.

Endpoints

The primary endpoints of the study assessed the best overall imaging response (BOR) to EV, as per RECIST v.1.1 [19]. Patients evaluable for response were defined as those who had baseline imaging and at least one set of imaging studies after initiation of EV treatment.

Statements and declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

BSK Honoraria: Angelini, Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, IPSEN, Janssen, Merck MSD, Novartis, Pfizer. All unrelated to the present paper.

JK Honoraria: Angelini, Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, IPSEN, Janssen, Merck MSD, Novartis, Pfizer, Research Funding: Novartis.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Results

The study included 16 patients aged between 47 and 80 years, whose time from diagnosis ranged 10.9–106.6 months (median 26.7 months), and who had been treated between 14th November 2022 and 25th November 2023. Notably, the time from metastatic disease to initiation of the EV was 9.6–37.9 months (median 13.9 months). Observation time (from the start of EV treatment to death or end of the study): 8–315 days (median 88 days). Time of EV treatment (from the start of EV to discontinuation/death/end of the study): 8–245 days (median 78 days).

Partial response, as the best overall response, was observed in 4 out of 9 (44%) patients who had imaging performed by the end of data collection. Two patients (22%) experienced progression as the best overall imaging response. Disease stabilization (DS) was achieved in

Table 1. Patients' characteristics

Parameters	Results in 16 patients treated with EV
Median (range) age at start of EV (years)	72 (47–82)
Male sex, *n* (5)	14 (87.5)
Ethnicity: white, *n* (%)	16 (100)
Median (range) BMI at start of EV [kg/m^2]	25.6 (18.6–32.8)
Current or former smoker, *n* (%)	2 (12.5)
Primary tumour site	
Bladder, *n* (%)	10 (62.5)
Renal pelvis, *n* (%)	4 (25.0)
Both, *n* (%)	1 (6.25)
Histology	
Pure transitional cell, *n* (%)	15 (93.8)
Neuroendocrine, *n* (%)	1 (6.2)
Grade	
High grade, *n* (%)	15 (93.8)
Low grade, *n* (%)	1 (6.2)
TNM at diagnosis	
T1, *n* (%)	2 (12.5)
T2, *n* (%)	5 (31.2)
T3, *n* (%)	1 (6.2)
T4, *n* (%)	8 (50.0)
N0, *n* (%)	4 (25.0)
N1, *n* (%)	3 (18.8)
N2, *n* (%)	6 (37.5)
Nx, *n* (%)	3 (18.8)
M0, *n* (%)	10 (62.5)
M1, *n* (%)	6 (37.5)
Median (range) time from diagnosis to metastatic disease (months)	8.4 (0–94.0)
Sites of metastasis at diagnosis of metastatic disease	
Lung, *n* (%)	8 (50.0)
Liver, *n* (%)	3 (18.8)
Lymph nodes, *n* (%)	10 (62.5)
Soft tissue, *n* (%)	2 (12.5)
Stomach, *n* (%)	1 (6.2)
Prostate, *n* (%)	1 (6.2)
Urethra, *n* (%)	1 (6.2)
Local recurrence, *n* (%)	1 (6.2)
Treatment before EV	
Neoadjuvant chemotherapy, *n* (%)	2 (12.5)
BCG for NMIBC, *n* (%)	3 (18.8)
Surgery	
Cystoprostatectomy, *n* (%)	5 (31.2)
Nephrectomy, *n* (%)	5 (31.2)
Cystectomy, *n* (%)	1 (6.2)
Adjuvant systemic therapy, *n* (%)	2 (12.5)
First-line chemotherapy for metastatic disease	
Cisplatin + gemcitabine, *n* (%)	10 (62.5)
Carboplatin + gemcitabine, *n* (%)	2 (12.5)
Other, *n* (%)	3 (18.8)
No first-line chemotherapy, early progression on neoadjuvant therapy	1 (6.2)
No data	1 (6.2)
Avelumab maintenance therapy, *n* (%)	11 (68.8)
Best response PR, *n* (%)	2 (12.5)
Best response DS, *n* (%)	3 (18.8)
Best response PD, *n* (%)	6 (37.5)
Progression, *n* (%)	9 (56.2)
Second-line immunotherapy, *n* (%)	5 (31.2)
Pembrolizumab, *n* (%)	1 (6.20
Nivolumab, *n* (%)	1 (6.2)
Atezolizumab, *n* (%)	1 (6.2)
Pembrolizumab + lenvatinib	1 (6.2)
ECOG performance score at the start of EV	
0, *n* (%)	1 (6.2)
1, *n* (%)	14 (87.5)
2, *n* (%)	1 (6.2)
Metastases at the start of EV	
Lung, *n* (%)	8 (50.0)
Bone, *n* (%)	2 (12.5)
Liver, *n* (%)	6 (37.5)
Soft tissue, *n* (%)	4 (25.0)
Lymph nodes, *n* (%)	13 (81.2)
Stomach, *n* (%)	1 (6.2)
Prostate, *n* (%)	1 (6.2)
Urethra, *n* (%)	1 (6.2)
Local recurrence, *n* (%)	1 (6.2)
Laboratory tests' results at the start of EV	
Median (range) haemoglobin, g/dl	11.4 (9.5–14.3)
Median (range) neutrophil count, × 103/µl	5.92 (1.64–10.38)
Median (range) lymphocyte count, × 103/µl	1.58 (0.62–2.77)
Median (range) NLR	3.75 (0.98–11.0)
Median (range) platelet count, × 103/µl	233 (102–518)
Median (range) PLR	173 (88–266)

BCG – bacillus calmette-guerin, BMI – body mass index, DS – disease stabilization, EV – enfortumab vedotin, NLR – neutrophile-lymphocyte ratio, NMBIC – for non-muscle-invasive bladder cancer, PLR – platelet-lymphocyte ratio, TNM – tumour-node-metastasis

3 patients (33%) CTCAE grade 3 and 4. Adverse events were observed in 3 out of 16 patients (18.75%), and 2 of those patients required dose reduction. Cutaneous toxicity required systemic therapy with corticosteroids and topical agents. Detailed information about the effectiveness and toxicity of treatment and additional therapies used is available in Table 2. At the time of data collection, 3 patients had developed disease progression.

Table 2. Treatment with enfortumab vedotin

Parameters	Results in 16 patients treated with EV
Standard EV dose at first administration, *n* (%)	16 (100)
G3–G4 adverse events, *n* (%)	3 (18.75)
Cutaneous toxicity, *n* (%)	1 (6.2)
Hyperglycaemia	1 (6.2)
No data, *n* (%)	1 (6.2)
Dose reduction, *n* (%)	2 (12.5)
Timing of dose reduction	
1–3 months from start, *n* (%)	1 (6.2)
No data, *n* (%)	1 (6.2)
Skipping dose due to toxicity, *n* (%)	1 (6.2)
Proton-pump inhibitor, *n* (%)	1 (6.2)
Insulin, *n* (%)	1 (6.2)
Steroids, *n* (%)	3 (18.8)
Antibiotics, n (%)	1 (6.2)
Best response	
PR, *n* (%)	4 (25.0)
DS, *n* (%)	3 (18.8)
PD, *n* (%)	2 (12.5)
No data, *n* (%)	7 (43.8)
Progression, *n* (%)	3 (18.8)
Death, *n* (%)	3
Radiotherapy, *n* (%)	3 (18.8)
Conventional or palliative, *n* (%)	2 (12.5)
Stereotactic, *n* (%)	1 (6.2)
Lymph nodes, *n* (%)	1 (6.2)
Bone, *n* (%)	2 (12.5)
Use of bone-targeted agents, *n* (%)	2 (12.5)

DS – disease stabilization, EV – enfortumab vedotin

Discussion

This study describes the effectiveness and tolerance of EV in the real-world setting in a population of 16 patients who had already exhausted all other available therapeutic options. The objective response rate was 44% (4/9), which is consistent with ORR in the EV-301 trial (41%) [15]. The EV-103 trial [14] compares the combination of EV with pembrolizumab vs. EV in monotherapy, and the EV-302 trial [20] compares that combination vs. chemotherapy. The combination of ADC and immune oncology (IO) seems to be a highly effective therapy with excellent ORR rates, and this therapeutic option can be used in aggressive forms of urothelial carcinoma, especially in patients without significant comorbidities. The enfortumab vedotin monotherapy arm achieved similar ORR to other clinical trials (45%) [14]. Modern oncology tends to use highly active therapies in the first line of treatment when patients can benefit the most and can cope with AE. Such trends are seen in renal cell carcinoma, where first-line treatment is IO in conjunction with vascular endothelial growth factor inhibitors (VEGFi) [21, 22].

Large multicentre retrospective cohort studies such as the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) [23] or the European Multicentre Real-world Patient Cohort [24] reported ORRs of 52% and 41.6%, respectively. These results are coherent with real-world experiences in the literature, e.g. Minato *et al*. described an ORR of 57.7% [25]. The median overall survival (mOS) and median progression-free survival (mPFS) in the clinical trial were 12.88 months (95% CI: 10.58–15.21) and 5.55 months (95% CI: 5.32–5.82), respectively [15]. Similar values were reached by Zschäbitz *et al*. with a mOS of 10.0 months (95% CI: 7.20–12.80) and a mPFS of 5.0 months (95% CI: 4.34–5.67) [24] as well as by Minato *et al*. with a mOS of 10.3 months (95% CI: 6.8–12) and a mPFS of 5.4 months (95% CI: 4–7.5) [25]. Interestingly, the UNITE study demonstrated longer values, with a mOS of 14.4 months (95% CI: 11.8–16.9) and a mPFS of 6.8 months (95% CI: 5.6–7.4) [23]. Due to the small sample size and a short-term follow-up, we were unable to present reliable mOS and PFS data. Only 22% of the patients in our study (2 out of 9, no data yet on 7 patients) had progressive disease as their best response, which corresponds to the results in the UNITE study (22%) [23].

The incidence of events of grade 3 or higher reached ≥ 25% in other real-world studies [24, 25] and 51.4% in the EV-301 trial [15]. The observed differences may be related to difficulties in collecting data retrospectively and differences in the extent of examination of patients. Notably, the patients included in this study had a long history of previous therapies and had used all available treatment options. The median age was 70 years, and the time from diagnosis to start of EV treatment was 10.9–106.6 months (median 26.7 months). Therefore, it appears that even heavily pretreated and frail patients can tolerate EV treatment and can achieve benefits from the therapy. Furthermore, it can be concluded from the EV-301 study that the frequency and severity of EV side effects are similar to those of chemotherapy (grade 3 or higher occurred in 51.4% vs. 49.8%, respectively) [15]. Hence, patients whose general condition allows them to receive chemotherapy could (if there are no contraindications specific to EV treatment) receive EV.

The most specific toxic effects of EV include neuropathy, hyperglycaemia, and skin reactions such as pruritus, maculopapular rash, and alopecia [14, 15, 26]. The prevalence of cutaneous side AE is related to the drug's mechanism of action, as there is a physiologically high expression of nectin-4 in the human epidermal keratinocytes and skin appendages [16, 17]. The bystander effect is another mechanism responsible for skin reactions. Enfortumab

vedotin endocytosis is followed by the release of the molecule responsible for inhibiting microtubules – MMAE – and its diffusion along the cell membrane, which causes apoptosis in adjacent tumour cells [27]. Notably, actively dividing epidermal keratinocytes are particularly susceptible to the MMAE, and disruption of their homeostasis is responsible for such toxicity [28]. Vlachou *et al*. observed that patients with cutaneous toxicity achieve higher ORR compared to patients without toxicity (57.7% vs. 24%, respectively, $p = 0.0145$). Furthermore, all patients who achieved complete response experienced skin reactions [26]. Education of both the health care practitioners and the patients seems to be an important part of treatment because early response to the first signs of skin reactions can prevent the development of dangerous toxicities [14].

Antibody-drug conjugates represent a class of innovative targeted therapy drugs designed for enhanced selectivity and potentially reduced off-target toxicity. As of 2023, 15 ADCs have been approved by the Food and Drug Administration (FDA) for the treatment of various solid tumours as well as haematological malignancies [29]. Since the first FDA approval of ADC in 2000, significant progress has been achieved in the field, as evidenced by hundreds of new ADCs currently under evaluation in clinical and preclinical trials. Among them are ADCs proposed for UC treatment, such as sacituzumab govitecan [30] and disitamab vedotin [31]. The former is especially worth mentioning considering the differences in toxicity between EV and sacituzumab govitecan, such as the potential to cause neuropathy. This may open an avenue for innovative therapy for patients who are not eligible for EV administration. In fact, with limited overlap in major toxicities between the 2 drugs, researchers are now seeking to assess whether sacituzumab govitecan can be used in combination with EV in metastatic UC [32]. Looking ahead, we may see a more personalized approach to cancer treatment and therefore expect better treatment efficacy when selecting for Trop2 overexpression. Furthermore, substantial advances are being made in the research of new types of antitumour-targeted drugs, including peptide-drug conjugates and immune-stimulating antibody conjugates.

Despite the constant progress in cancer therapy, drug resistance remains a major obstacle to overcome. Multiple mechanisms of this process have been reported including antigen-related resistance, failure in internalisation into the cancer cell, impaired lysosomal function, or drug-efflux pumps [33]. In the case of EV treatment, the main issue is a decreased membranous Nectin-4 expression. Klümper *et al*. showed that Nectin-4 expression lowers during the metastatic spread of UC, which results in resistance to EV therapy [34]. Weak or absent expressions were strictly correlated with shorter PFS. It is worth noting that in spite of decreased nectin-4 expression the expression of TROP2 (a target for sacituzumab govitecan) remains significantly higher, so that EV-resistant cells may remain sensible to SG [35]. Moreover, several attempts to overcome the resistance to anti-nectin-4 ADC are being made. Cabaud *et al*. in a preclinical trial with mouse models managed to restore sensitivity to EV in vitro by P-glycoprotein pharmacological inhibitors such as tariquidar [36]. Although the findings need further examination, they open new opportunities for overcoming drug resistance in UC therapy.

In this study, all 3 patients who experienced disease progression during EV treatment were eligible for paclitaxel as the next line of treatment, but only 2 received the therapy. Curran *et al*. reported that only 51% of patients received therapy post-EV, and patients who did not receive treatment had significantly worse mOS (median 43.1 vs. 16.9 weeks, $p = 0.015$) [37]. Particularly noteworthy is the fact that 44% of all therapies were clinical trials, which may further exaggerate the results obtained, but at the same time it gives us hope for further effective therapies.

The coming years may bring many changes in the urothelial cancer therapy. The treatment of metastatic and advanced UC has been and will continue to be a formidable challenge, but access to modern drugs will make treatment more effective. Immunotherapy and ADC provide the opportunity to tailor treatment for the individual patient and offer the possibility of sequencing therapy to maximize outcomes. Erdafitinib is another step toward personalized treatment and shows efficacy in FGFR-altered UC.

Conclusions

Enfortumab vedotin demonstrates potential as an effective, tolerable treatment strategy for advanced UC patients who have already exhausted standard treatment options. As experiments and researchers continue to personalize UC treatment, we anticipate further advancements in the application of ADC.

The authors declare no conflict of interest.

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Submitted: 18.12.2023
Accepted: 31.12.2023