ACCSCIENCE PUBLISHING

Tumor Discovery

CASE REPORT

Complete response after two cycles of enfortumab vedotin in a patient with metastatic bladder cancer: A case report

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Abstract

Metastatic urothelial carcinoma, the most common subtype of advanced bladder cancer, remains associated with poor outcomes and limited treatment options despite systemic therapies. Enfortumab vedotin (EV), an antibody-drug conjugate targeting Nectin-4, has shown significant improvements in progression-free and overall survival in platinum- and immunotherapy-pretreated patients, as demonstrated in the EV-201 and EV-301 trials. In this report, we present a case of a patient who had previously received platinum-based neoadjuvant chemotherapy and experienced disease progression under nivolumab maintenance therapy but subsequently achieved a complete response in a short period with EV treatment. EV has emerged as a valuable treatment alternative in this aggressive disease, where survival expectations are generally poor. However, questions remain regarding which patients benefit most from the treatment and whether the response is correlated with nectin-4 expression levels.

Keywords: Metastatic urothelial carcinoma; Enfortumab vedotin; Complete response

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1. Background

Non-muscle invasive bladder cancer accounts for approximately 75% of all bladder cancer cases, while muscle-invasive bladder cancer (MIBC) accounts for the remaining 25%. Although the rate of metastatic disease is around 5% at the time of diagnosis, distant metastases can develop in up to 50% of patients during follow-up despite receiving radical treatments, especially in patients diagnosed with MIBC.[1]

Metastatic urothelial carcinoma (mUC) is the most common histological subtype of advanced bladder cancer.[2] Despite systemic treatment approaches, mUC remains associated with poor survival outcomes and limited therapeutic options. Platinum-based chemotherapy protocols have long been accepted as the standard approach for the first-line treatment of metastatic disease; however, many patients develop non-response or relapse. While the use of immunotherapy in mUC has expanded in recent years, effective targeted therapies are still lacking for those who develop resistance or do not derive sufficient clinical benefit from these agents.[3,4]

Enfortumab vedotin (EV) is an antibody-drug conjugate targeting Nectin-4, a protein highly expressed in urothelial carcinoma cells. Upon binding to nectin-4 on the tumor

cell surface, EV is internalized and releases the cytotoxic agent monomethyl auristatin E, disrupting microtubule formation and leading to tumor cell death by apoptosis.[5] Phase II EV-201 and Phase III EV-301 clinical trials have shown significant benefits on progression-free survival (PFS) and overall survival (OS) among patients with locally advanced or mUC who had previously received platinum-based chemotherapy and programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor therapy.[6,7] Given the significance of the findings from these studies, EV has emerged as an important treatment option for treatment-resistant mUC. In this context, we present a case of metastatic bladder cancer treated with EV.

2. Case presentation

A 66-year-old male patient with a known history of arterial hypertension, managed with amlodipine 10 mg daily, and a 40-pack-year smoking history, presented to our institution with a 3-month history of painless hematuria, which had gradually increased in frequency. Ultrasonography revealed a malignant lesion on the left side wall of the bladder with increased thickness extending into the bladder lumen. The patient subsequently underwent transurethral resection of the bladder tumor. Histopathological analysis of the transurethral resection of the bladder tumor specimen revealed high-grade urothelial carcinoma with a pathological stage of at least T2. Staging with positron emission tomography/computed tomography (PET/CT) revealed abnormal bladder wall thickening and multiple lymph nodes in the perivesical, internal, and external iliac regions suspicious for malignancy; however, no distant metastases were detected. Based on the diagnosis of locally advanced bladder cancer, the patient received neoadjuvant chemotherapy consisting of gemcitabine (1,000 mg/m^2 on days 1 and 8) and cisplatin (70 mg/m^2 on day 1) in a 21-day cycle for a total of four cycles. The patient subsequently underwent radical cystectomy with pelvic lymph node dissection, followed by orthotopic neobladder reconstruction. Final pathology revealed ypT3N2, indicating post-neoadjuvant therapy pathological staging with tumor invasion into perivesical tissue (T3) with involvement of multiple regional lymph nodes (N2), consistent with high-grade urothelial carcinoma. Due to the presence of residual tumor, adjuvant treatment with nivolumab was initiated at a dose of 240 mg every 2 weeks.

At the 9th month of treatment, a follow-up PET/CT scan revealed increased 18 F-fluorodeoxyglucose (FDG) uptake in several regions. A 12 × 16 mm lymph node located in the right lateral aspect of the mesorectum adjacent to the rectum demonstrated a maximum standardized uptake value (SUVmax) of 7.8. Additional FDG-avid soft tissue foci were observed adjacent to the left external iliac vascular structures (SUVmax: 6.5) and in the right mesorectal fascia (SUVmax: 4.9). A soft tissue mass measuring 18 × 34 × 30 mm extending from the right side of the mesorectum to the right mesorectal fascia at the level of the coccyx showed intense FDG uptake (SUVmax: 13.6). Furthermore, increased pathological FDG uptake was noted in the soft tissue adjacent to the posterior aspect of the symphysis pubis (SUVmax: 5.5). PET/CT images are presented in Figure 1.

Following these findings, the patient was initiated on EV at a dose of 1.25 mg/kg administered on days 1, 8, and 15 of a 28-day cycle. After two cycles, follow-up PET/CT imaging demonstrated near-complete to complete morphological and complete metabolic regression of previously identified metastatic lesions. Specifically, resolution was noted in lymphadenopathy located in the right common iliac area, right mesorectal fascia and its vicinity, and the posterior aspect of the symphysis pubis, compared to the prior scan. PET/CT images are shown in Figure 2. During treatment, the patient experienced grade 1 peripheral neuropathy and grade 1 cutaneous reactions. These adverse events were mild and did not necessitate any dose modifications. As of the 9th month of treatment, the patient remains on EV, with no radiologically detectable lesions, and maintains a complete response.

3. Discussion

EV has emerged as a valuable treatment option for patients with mUC who have previously received platinum-based chemotherapy and PD-1/PD-L1 inhibitor therapy, demonstrating significant response rates and survival

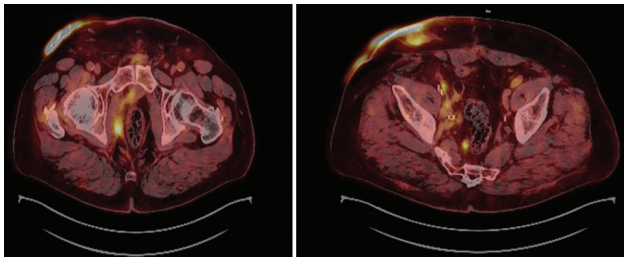

Figure 1. Positron emission tomography-computed tomography images obtained prior to the initiation of enfortumab vedotin therapy

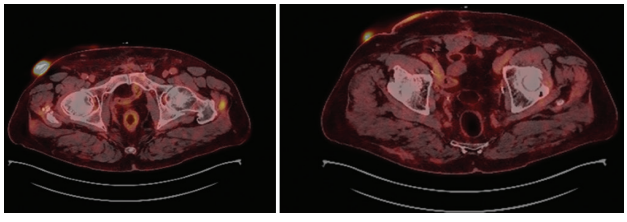

Figure 2. Positron emission tomography-computed tomography images obtained after two cycles of enfortumab vedotin therapy

benefit. As an antibody-drug conjugate targeting nectin-4, it offers high tumor selectivity and, as observed in our case, can induce a rapid therapeutic response, making it an effective targeted approach in heavily pretreated patients. To the best of our knowledge, our case represents one of the most rapid complete responses to EV reported in the literature for mUC. This case may serve as a valuable reference, particularly in symptomatic patients or those requiring a prompt therapeutic response.

EV was first evaluated in the single-arm phase 2 trial EV-201, where it demonstrated promising outcomes in mUC patients previously treated with platinum-based chemotherapy and immune checkpoint inhibitors. The study reported a median PFS of 5.8 months and a median OS of 11.7 months.[6] Subsequently, the phase 3 EV-301 trial compared EV with standard chemotherapy options in a similar patient population. EV achieved a median OS of 12.88 months versus 8.97 months with chemotherapy and a median PFS of 5.55 months versus 3.71 months, respectively. In addition, the complete response rate in the EV arm was 4.9%, with a disease control rate of 71.9%.[7] In our case, the patient had previously received platinum-based neoadjuvant chemotherapy and experienced disease progression under maintenance of nivolumab. Notably, a complete response was achieved following treatment with EV.

The median time to response for EV was reported as 1.8 months in the EV-201 trial and 1.41 months in the EV-301 trial.[6,7] These findings suggest that EV provides a rapid and effective tumor response in patients with mUC. However, neither study specified the exact time at which a complete response was achieved among responders.[6,7] In our case, a complete response was observed after two cycles (approximately 2 months) of treatment.

Immunotherapeutic agents have gained a significant role in the treatment algorithm of mUC by markedly improving OS, particularly through the use of PD-1 and PD-L1 inhibitors. For cisplatin-ineligible patients with mUC, first-line immunotherapy options include atezolizumab, as demonstrated in the IMvigor210 trial,[8] and pembrolizumab, as shown in the KEYNOTE-052 trial.[9] Pembrolizumab has shown an OS benefit in patients with disease progression after platinum-based chemotherapy, as demonstrated in the KEYNOTE-045 trial.[10] Similarly, nivolumab demonstrated efficacy as a second-line treatment in the CheckMate 275 trial.[11] In addition, avelumab provided a survival advantage as a maintenance therapy in patients who responded to platinum-based chemotherapy, according to the findings of the JAVELIN Bladder 100 trial.[12] The CheckMate 274 trial demonstrated that adjuvant treatment with nivolumab significantly prolonged disease-free survival in high-risk patients following radical cystectomy.[13] Although the indications and sequencing of PD-1/PD-L1 inhibitors can be complex, immunotherapy remains a critical component of treatment for nearly all patients with mUC at some stage of their disease course. In line with the CheckMate 274 trial, our patient had also received adjuvant nivolumab following radical cystectomy.

Following the favorable responses observed with PD-1/PD-L1 inhibitors and EV, the EV-302/KEYNOTE-A39 trial was conducted to evaluate the efficacy of the combination of EV and pembrolizumab as a first-line therapy in patients with mUC. Compared to standard treatments, the combination demonstrated significant improvements in both PFS and OS, positioning this regimen as a potentially new standard of care.[14]

Although our case demonstrates a favorable response to EV, serving as a positive example for both clinicians and patients, this observation is limited to one patient. Questions remain regarding which subgroups of patients are more likely to benefit from EV therapy. In particular, further research is needed to elucidate the relationship between Nectin-4 expression levels and treatment response and identify novel predictive biomarkers that will refine patient selection and improve prognostic assessment in the future.

4. Conclusion

Although various treatment modalities, such as chemotherapy, immunotherapy, and targeted agents, have expanded in the management of mUC, the overall prognosis remains poor. EV has emerged as a valuable treatment alternative in this aggressive disease, where survival expectations are generally poor. However, questions remain regarding patient selection and the potential correlation between treatment response and nectin-4 expression levels. Addressing these uncertainties will require future studies involving larger patient cohorts and comprehensive subgroup analyses.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Ali Kaan Güren

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Investigation: Ali Kaan Güren, Murat Sari
Methodology: Murat Sari, Osman Köstek
Writing – original draft: Ali Kaan Güren
Writing – review & editing: Murat Sari, Osman Köstek

Ethics approval and consent to participate

The patient gave written informed consent prior to participation.

Consent for publication

The patient provided written informed consent for the publication of anonymized data collected during the study. For person data included in this manuscript (such as quotes, images, or case details), consent for publication has been obtained. Identifiable information has been removed or anonymized to protect the privacy of participants.

Availability of data

Data will be made available upon reasonable request from the corresponding author.

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