



Case report

Neoadjuvant therapy with Disitamab vedotin in treating muscle-invasive bladder cancer: A case report



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ARTICLE INFO

Keywords:

Neoadjuvant therapy
Muscle-invasive bladder cancer
Disitamab vedotin
HER2-Targeted
Antibody-drug conjugates

ABSTRACT

Purpose: Platinum-based regimens are regarded as the preferred alternative for neoadjuvant chemotherapy for muscle-invasive bladder cancer (MIBC) patients. However, some patients cannot tolerate platinum-based regimens. We report an MIBC case with severe renal insufficiency treated by neoadjuvant therapy with gemcitabine and Disitamab Vedotin.

Materials and Methods: A 68-year-old man with severe renal insufficiency was admitted to our department and diagnosed with cT3N0M0 MIBC. Immunohistochemical staining of the biopsy tissues showed human epidermal growth factor receptor 2 expression (1+). This patient received neoadjuvant therapy with gemcitabine 1600 mg and DV 120 mg intravenously every three weeks 3 times. We compared the imaging results of the patient before and after neoadjuvant therapy. In addition, the white blood cell count, alanine aminotransferase, aspartate aminotransferase, and serum creatinine were followed up during neoadjuvant therapy. Abnormal symptoms such as hair loss, fatigue, and hypoesthesia were also recorded.

Results: According to the imaging examinations, the lesions were significantly reduced after receiving neoadjuvant therapy. Significant adverse side effects did not occur during neoadjuvant therapy.

Conclusions: In this T3N0M0 cisplatin-ineligible patient, gemcitabine combined with DV as neoadjuvant therapy achieved radiological partial response, and no significant adverse events were observed during neoadjuvant therapy.

1. Introduction

Bladder cancer is the tenth most prevalent cancer worldwide and is much more common in males than in females [1]. Histologically, it is classified as muscle-invasive bladder cancer (MIBC) or nonmuscle-invasive bladder cancer (NMIBC) [2]. Transurethral resection of bladder tumor (TURBT) and postoperative bladder perfusion therapy are recommended for NMIBC patients. For MIBC patients, neoadjuvant chemotherapy (NAC) combined with radical cystectomy (RC) and pelvic lymph node dissection (PLND) is usually recommended. In NAC, cisplatin-based multiagent neoadjuvant chemotherapy shows 5% and 9% absolute improvement in

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5-year overall survival (OS) and disease-free survival (DFS), respectively [3], and it is regarded as the preferred and recommended regimen by clinical guidelines [4–6]. However, platinum agents have certain nephrotoxicity. For cisplatin-ineligible MIBC patients, chemotherapy is contraindicated according to the European Society for Medical Oncology and National Comprehensive Cancer Network guidelines. For such patients, cystectomy alone is recommended. Neoadjuvant immunotherapy, such as programmed cell death protein 1/programmed cell death 1 ligand 1 (PD1/PDL1) inhibitors, is only recommended in clinical trials. HER2-targeted agents have also been reported to treat bladder cancer [7]. Here, we report an MIBC patient with pathologically confirmed human epidermal growth factor receptor 2 (HER2) (1+) by immunohistochemistry (IHC) in biopsy tissues. This patient received neoadjuvant therapy with gemcitabine combined with Disitamab Vedotin (DV), a novel antibody–drug conjugate (ADC) of HER2. This was the first reported case to receive such a regimen worldwide.

2. Case presentation

A 68-year-old man was admitted to our hospital on January 16, 2022, because of intermittent painless gross hematuria for 4 months. He was diagnosed with severe coronary atherosclerotic heart disease and received percutaneous coronary intervention 4 months prior. In addition, he had a history of hypertension for 3 years and type 2 diabetes for almost 20 years. On admission, the estimated glomerular filtration rate was 21.4 ml/min/1.73 m², and the creatinine level was 255 μmol/L, which was considered to indicate chronic kidney disease 4 [8]. Magnetic resonance imaging (MRI) showed that the lesion was located in the inferior and right posterior walls of the bladder, with a maximum diameter of 8.8 cm, invading the right ureter. No enlarged lymph node or pelvic bone destruction was identified [Fig. 1(A and B)]. According to the imaging findings, this patient was clinically considered to have MIBC and classified as cT3N0M0.

For pathological diagnosis, transurethral resection of bladder tumor was performed on January 18. During the operation, the right ureteral orifice was invisible. The right lateral wall of the bladder was covered with a cauliflower-like neoplasm, which also covered the right ureteral orifice and invaded the right bladder neck and part of the anterior wall. Part of the tumor on the right lateral bladder wall was resected and sent for pathological examination. To identify potential therapeutic targets, IHC staining for HER2 was performed. Fluorescence in situ hybridization (FISH) of HER2 was not performed. This patient was pathologically confirmed to have invasive high-grade papillary urothelial carcinoma of the bladder with HER2 (IHC 1+) [Fig. 2(A and B)], positive control is provided as Supplementary Fig. S1.

Subsequently, with the patient's consent, this patient received gemcitabine 1600 mg and DV 120 mg intravenously every three weeks 3 times (January 23, February 12 and March 7, 2022, respectively). The results of the blood test during therapy are provided in Fig. 3(A–D). Blood pressure and blood glucose were stable during neoadjuvant therapy. In addition, during neoadjuvant therapy, adverse events, such as hair loss, fatigue, and hypoesthesia, also did not occur, which indicated level 1 according to the Common Terminology Criteria for Adverse Events 5.0.

Approximately two months later, another preoperative MRI was arranged on April 2, which suggested that the lesion was significantly smaller than before, with a maximum diameter of 4.0 cm, which indicated partial response according to the Response Evaluation Criteria In Solid Tumors 1.1 [9]. The invasion of the right lower ureter was obviously reduced [Fig. 4(A and B)]. Then, RC with PLND was performed on April 12, 2022, and the postoperative pathological findings proved high-grade invasive urothelial carcinoma involving the bladder lamina propria with HER2 (IHC 1+) [Fig. 5(A and B)].

After the surgery, the patient was followed up every 3 months, and the last follow-up date was February 10, 2023. During the postoperative follow-up, this patient did not receive other anticancer therapies. Cancer relapse did not occur according to the CT scan. Renal function, blood pressure and blood glucose remained stable.

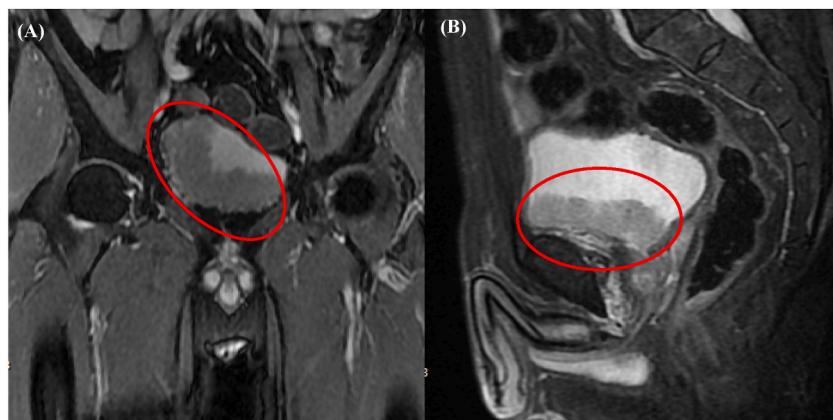


Fig. 1. Magnetic resonance imaging scanning of the bladder before transurethral resection of bladder tumor. (A) Coronal plane; (B) sagittal plane.

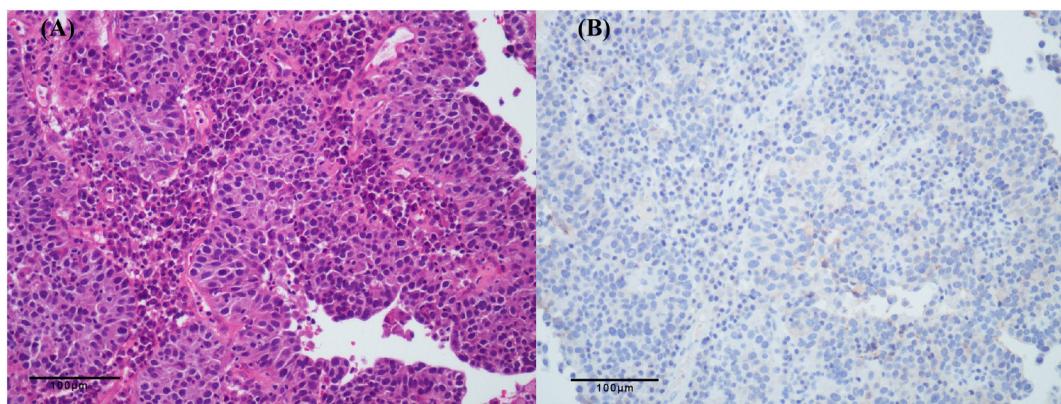


Fig. 2. Representative hematoxylin-eosin staining of tumor tissues from transurethral resection of bladder tumor (A), magnification: $\times 200$. Representative immunohistochemical staining for HER2 in tumor tissues from transurethral resection of bladder tumor (B), magnification: $\times 200$.

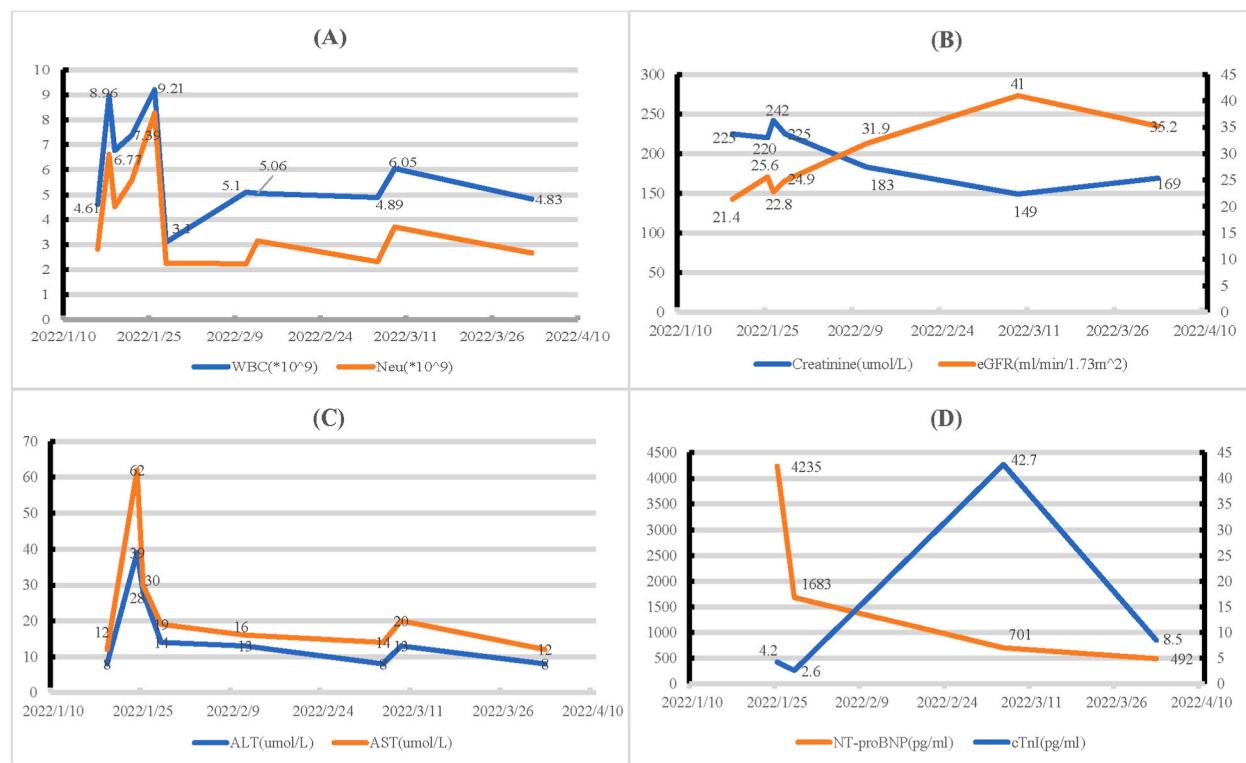


Fig. 3. The results of blood tests during neoadjuvant therapy. WBC: White blood cell, Neu: Neutrophil count (A). Creatinine, eGFR (B). ALT, AST (C). NT-proBNP, cTnI (D). eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, NT-proBNP: N-terminal pro-B-type natriuretic peptide, cTnI: cardiac troponin I.

3. Discussion

Bladder cancer is the most common cancer in the urinary system [10]. Approximately 25% of new cases are MIBC or metastatic disease [11]. Neoadjuvant chemotherapy, also called preoperative chemotherapy, can downstage the lesion and eliminate micro-metastases, thereby improving long-term postoperative survival [12]. For patients with MIBC classified as cT2~4aNOM0, RC with PLND after NAC remains the most recommended treatment option [6]. The first-line regimens recommended by major guidelines for NAC include cisplatin combined with gemcitabine or DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with granulocyte colony-stimulating factor [5,6]. Cisplatin-ineligible patients were defined as those with at least one of the following [13]: performance status >1; GFR <60 ml/min; grade >2 audiometric hearing loss; grade >2 peripheral neuropathy or New York

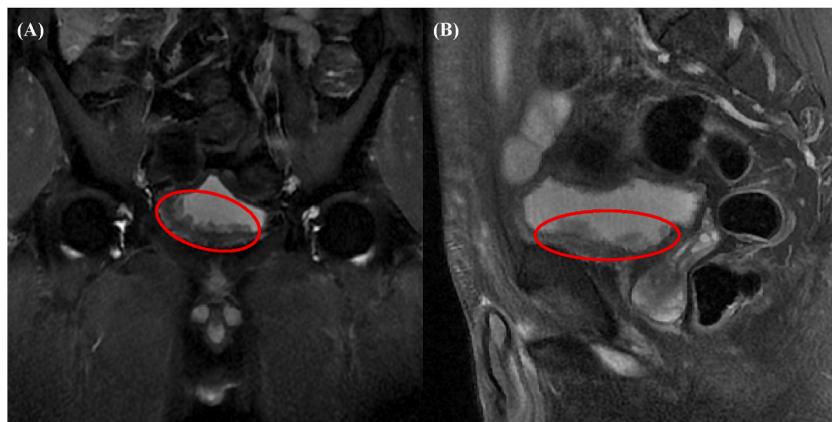


Fig. 4. Magnetic resonance imaging scanning of the bladder after neoadjuvant therapy. (A) Coronal plane; (B) Sagittal plane.

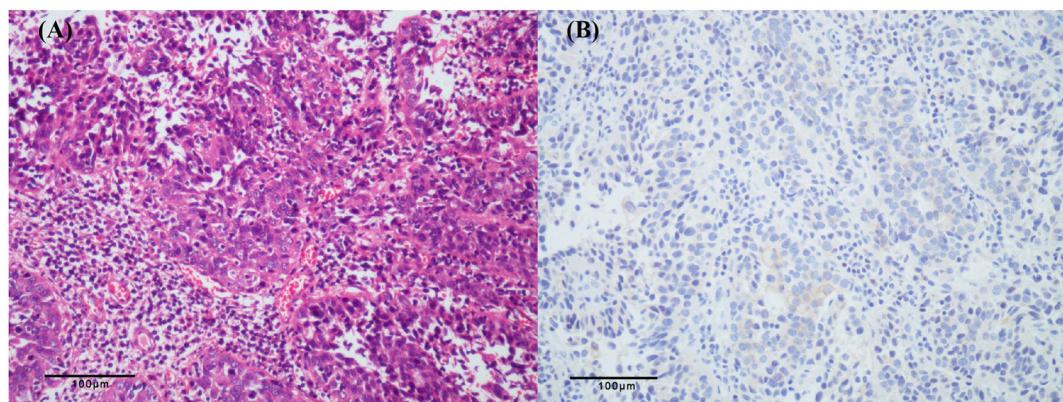


Fig. 5. Representative hematoxylin-eosin staining of tumor tissues from radical cystectomy (A), magnification: $\times 200$. Representative immunohistochemical staining for HER2 in tumor tissues from radical cystectomy (B), magnification: $\times 200$.

Heart Association class III heart failure. In the chemotherapy of metastatic bladder urocarcinoma, the use of carboplatin is recommended for some cisplatin-ineligible patients in major guidelines [4–6]. However, in NAC, it is not mentioned. Immunotherapy, such as pembrolizumab or atezolizumab, is reported to treat PDL1-positive, unresectable, metastatic and platinum-ineligible bladder cancer patients [14,15]. In those two trials, patients with GFR <30 ml/min were regarded as ineligible for pembrolizumab or atezolizumab. They are also reported as neoadjuvant immunotherapy in bladder cancer [16,17], but those patients are not specifically cisplatin intolerant. Neoadjuvant immunotherapy is recommended for MIBC patients within a clinical trial setting. The role of neoadjuvant immunotherapy for platinum-ineligible patients remains to be investigated.

HER2 is a transmembrane receptor of human epithelial growth factor. It consists of three regions, including an *N*-terminal extracellular domain (ECD), a single α -helical transmembrane domain, and an intracellular tyrosine kinase domain. The main function of HER2 is to heterodimerize with other receptors, such as HER1, HER3 or HER4. After that, the intracellular tyrosine kinase domain of HER2 can activate intracellular signaling pathways, such as the phosphatidylinositol-3-kinase signaling pathway, mitogen-activated protein kinase signaling pathway and phospholipase C-gamma signaling pathway, and regulate metabolism and proliferation in normal cells [18]. In tumor tissues, such as gastric and gastroesophageal junction cancers, breast cancer, biliary tract cancer, colorectal cancer, non-small cell lung cancer and bladder cancer, the amplification and overexpression of HER2 often exist, which can lead to persistent hyperactive cellular network signaling, resulting in abnormal cell proliferation [19]. To target the HER2-mediated signaling pathway, a variety of drugs have been designed, including ECD-binding antibodies (trastuzumab and pertuzumab), tyrosine kinase inhibitors (neratinib and lapatinib), bispecific antibodies, and ADCs (ado-trastuzumab emtansine, trastuzumab deruxtecan, and DV) [7]. At present, these drugs are mainly used for the treatment of breast cancer and gastroesophageal cancer with positive HER2 expression [20,21]. For urothelial carcinoma, a systematic review summarized the treatment effects of using single HER2-targeting agents, HER2-targeting agents combined with cytotoxic chemotherapy, dual HER2 blockades, or HER2-targeting ADCs. This systematic review concluded that ADCs are the most promising strategy [22].

ADCs are usually composed of three parts: antibody, linker and cytotoxic payload [23]. DV adopts a novel HER2 monoclonal antibody, Hertuzumab, which has a great affinity for HER2 targets and has the potential to treat cancers with low or even unstable

HER2 expression [24]. The cytotoxic payload of DV is monomethyl auristatin E (MMAE) [25], a small molecule tubulin depolymerizer. It can be delivered to tumor tissues after targeting antibodies. Then, endocytosis occurs and leads to agent internalization. MMAE can be released after linker cleavage and binds to tubulin, which inhibits polymerization and triggers apoptosis. Additionally, DV has a considerable bystander effect on nearby cells, which can help kill tumor cells with low or no HER2 expression for intratumoral heterogeneity [26]. In addition, this drug can also inhibit HER2-mediated signaling pathways and mediate antibody-dependent cell-mediated cytotoxicity, simultaneously inhibiting tumor cell proliferation [27].

Currently, in China, the approved indications of DV only include locally advanced or metastatic gastric or gastroesophageal junction cancer with HER2 overexpression (IHC 2,3+). DV should be used as a second-line therapy. A phase II trial of DV, which enrolled patients with locally advanced or metastatic gastric or gastroesophageal junction cancer, showed promising outcomes. The objective response rate (ORR) was 24.8%. The median progression-free survival (PFS) and OS were 4.1 months and 7.9 months, respectively [28]. In a case [29], it was reported that DV in a 52-year-old HER2 (2+) patient with advanced lung adenocarcinoma after failure of first-line therapy improved both lung lesions and brain lesions. For urothelial carcinoma, a multicenter, single-arm clinical study enrolled 43 HER2-positive patients (IHC 2+ or 3+) with locally advanced or metastatic urothelial carcinoma who previously failed at least one line of systemic chemotherapy. These patients were treated with DV at 2.0 mg/kg alone once every 2 weeks until disease progression, intolerable toxicity, death, or withdrawal of consent. The ORR was 51.2%, and the median PFS and OS were 6.9 months and 13.9 months, respectively [30]. In addition, a phase I study of DV showed an ORR of 35.7% in solid carcinomas with HER2 IHC 2+/FISH- [31]. Another clinical trial was conducted to evaluate the efficacy and safety of intravenous DV in patients with locally advanced or metastatic HER2-negative urothelial carcinoma (NCT04073602). At the date cutoff, the ORR was 26.3%, median PFS was 5.5 months and median OS was 16.4 months. A phase 1b/II trial of DV combined with toripalimab in patients with locally advanced or metastatic urothelial carcinoma (NCT04264936) showed a confirmed ORR of 50% for HER2 (- or 1+) & PD-L1 (+) and 50% for HER2 (- or 1+) & PD-L1 (-) at the date cutoff. These results suggest that DV has therapeutic prospects in patients with urothelial carcinoma with low or high HER2 expression. These promising results for HER2-negative tumors inspired us to tentatively use DV in this case.

In addition, a study showed that previously untreated metastatic urothelial carcinoma patients who were treated with gemcitabine alone obtained an ORR of 28% [32]. Two other studies showed that using gemcitabine combined with paclitaxel in NAC for previously untreated patients with high-grade urothelial carcinoma achieved ORRs of 37% and 69%, respectively, which suggested that gemcitabine combined with other agents may gain a better therapeutic effect [33,34]. We first used gemcitabine and DV as neoadjuvant therapy in this MIBC patient to assess the therapeutic efficiency, which has not been reported elsewhere.

The patient in our report was diagnosed with T3N0M0 MIBC. The imaging results before neoadjuvant therapy showed that the maximum diameter of the lesion was approximately 80 mm. After neoadjuvant therapy with DV and gemcitabine, the lesion significantly shrank. During neoadjuvant therapy, white blood cell count, alanine aminotransferase, aspartate aminotransferase, creatinine, estimated glomerular filtration rate, cardiac troponin I, and *N*-terminal pro-B-type natriuretic peptide were followed up. The results showed that the indicators above were not significantly worsened. In addition, the patients did not suffer from obvious drug-related adverse symptoms. Notably, serum creatinine was decreased during therapy. Therefore, gemcitabine combined with DV in neoadjuvant therapy was effective and safe for this patient.

4. Conclusion

In this T3N0M0 cisplatin-ineligible patient, gemcitabine combined with DV as neoadjuvant therapy achieved radiological partial response, and no significant adverse events were observed during neoadjuvant therapy.

Patient perspective

Written informed consent for publication was obtained from this patient.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding statement

This work was supported by the National Natural Science Foundation of China [grant number 81702989] to Chunguang Yang.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.heliyon.2023.e15157>.

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