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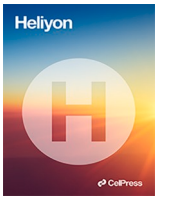

Case report

Downstaging guided neoadjuvant strategy shift and bladder preservation in locally advanced bladder cancer: A case report

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ABSTRACT

Background: The study of bladder preservation for muscle-invasive bladder cancer (MIBC) mainly focuses on the T2 stage, which remains difficult in the T3 and T4 stage. Pembrolizumab has been applied as neoadjuvant therapy followed by radical cystectomy for MIBC, gaining encouraging results in the phase II study. Disitamab vedotin, an antibody-drug conjugate (ADC), also achieved promising efficacy for refractory bladder cancer. However, the neoadjuvant therapy strategy of these drugs for bladder sparing remains further exploration.

Case presentation: A patient with locally advanced MIBC at our institute underwent a neoadjuvant therapeutic regimen followed by transurethral resection of bladder tumor (TURBT) and concurrent chemoradiotherapy. In light of limited initial efficacy, we enacted an adaptive shift in the neoadjuvant treatment strategy, transitioning from a combination of gemcitabine, *cis*-platinum, and pembrolizumab to disitamab vedotin with pembrolizumab. This approach ultimately achieved bladder preservation, complete response, and a remarkable 1-year disease-free survival (DFS).

Conclusion: Proactive evaluation in the early stages of tumor downstaging can serve as a guiding principle for neoadjuvant strategies. This is the first successful case of neoadjuvant pembrolizumab combined with disitamab vedotin and chemotherapy in MIBC patients achieving complete response and bladder preservation.

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1. Introduction

According to NCCN guidelines, the standard treatment of MIBC is platinum-based neoadjuvant chemotherapy combined with radical cystectomy and lymph node dissection [1]. For MIBC patients, especially those in the T2 stage, maximal TURBT with concurrent chemoradiotherapy for bladder preservation is also recommended [1]. Regarding patients in the T3 and T4 stages, preserving the bladder is currently a clinical challenge. Among them, the neoadjuvant therapy may achieve significant tumor downstage. In our previous study, the patient undergoing neoadjuvant chemotherapy for bladder cancer of T2-T4 achieved a downstaging rate of 52.5% (31/59) to a stage less than T1. Ultimately, 59.3% (35/59) of patients successfully preserved their bladder with an acceptable prognosis [2]. For these patients, the combination of neoadjuvant therapy, maximal TURBT, and concurrent chemoradiotherapy could be a feasible alternative, rendering it a promising avenue for future research.

Pembrolizumab showed a significant impact in a phase II study. Among patients with a combined positive score (CPS) $\geq$10, 54.3% achieved T0, while those with CPS $\leq$10 only had a lower rate of 13.3% [3]. Yet, the phase III study of PD-1 inhibitor neoadjuvant monotherapy is still under recruiting. ADC drugs are highly effective in advanced urothelial carcinoma, and they may even outperform chemotherapy. Disitamab vedotin is an ADC drug targeting HER2, which was independently developed in China. In refractory metastatic bladder cancer, disitamab vedotin achieved an overall response rate (ORR) of 47%. When combined with toripalimab, the ORR and disease control rate (DCR) reached 80% and 90% [4]. Moreover, several clinical trials (NCT05239624 and NCT05723991) have been launched to investigate whether ADC drugs can further improve their efficacy for neoadjuvant therapy of bladder cancer.

The current article reports the case of a 63-year-old male diagnosed with HER2 (3+) and PD-L1 (+) expression, who faced recurrent MIBC (T3b) following treatment with TURBT and Bacillus Calmette-Guerin (BCG) immunotherapy. Despite the recurrence, the patient was determined to preserve his bladder. In this scenario, we conducted an exploration of drugs and neoadjuvant treatment strategies. This case exemplifies the feasibility of tumor downstaging-guided neoadjuvant therapy, showcasing its potential to achieve bladder preservation in the context of locally advanced bladder cancer.

2. Case presentation

In February 2022, a 63-year-old male patient was admitted to our institution with a chief complaint of intermittent painless hematuria for 2 months. He had been suffering from hypertension and diabetes for 1 year, and both conditions were under regular treatment. The blood pressure and glucose levels were all well controlled. He had been smoking for 50 years but he had quit at the time

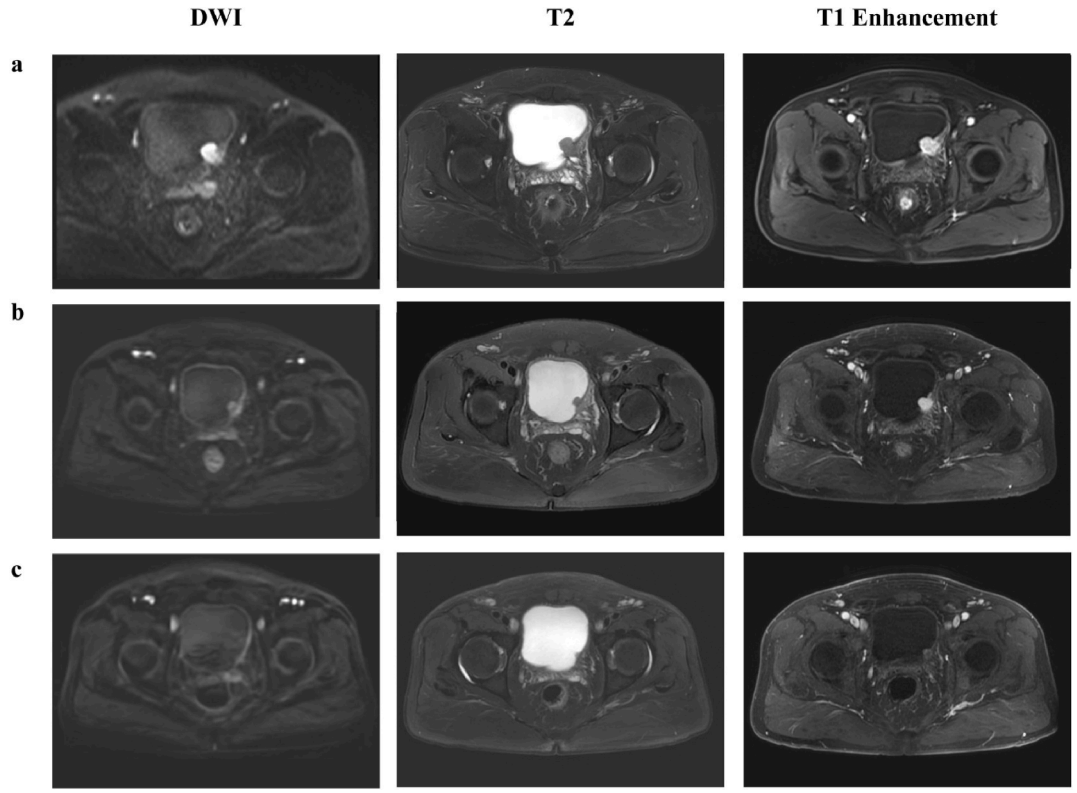

Fig. 1. MRI images tracking changes in the bladder wall during neoadjuvant therapy. a) Local recurrence of bladder cancer before treatment. b) Image of bladder lesion after two cycles of pembrolizumab + gemcitabine and cisplatin, the tumor was slightly shrunken. c) The evaluation of pembrolizumab + disitamab vedotin after two cycles treatment, the mass was obviously shrunk and the extravesical invasion was invisible.

of diagnosis.

Cystoscopy and pelvic magnetic resonance imaging (MRI) revealed a single tumor located in the left posterior wall of the bladder, with a maximum diameter of 3cm. No swollen lymph nodes or extravesical invasion were seen in the pelvis. Chest computed tomography (CT) showed no abnormalities, and CT urography (CTU) revealed no lesions in the upper urinary tract. Suspected of having a malignant bladder tumor, the patient underwent TURBT at our institution and immediate gemcitabine irrigation was administered on February 24th, 2022. The pathology of the specimen indicated high-grade invasive urothelial cancer. The tumor had infiltrated lamina propria but had not reached the detrusor muscle (pT1). There was no evidence of carcinoma in situ (CIS), lymphovascular invasion (LVI), or variant histology. Additionally, it tested positive for AE1/AE3 (2+), HER2 (3+), and PD-L1 (22C3) (positive, CPS:2). After surgery, regular bladder irrigation of BCG was administered.

In 2022 May, thoracoabdominopelvic CT and pelvic MRI conducted at our hospital revealed diffuse and inhomogeneous thickening of the bladder wall. The thickest part measured approximately 1.6 cm, and a 2.3*1.9 cm nodule was visible on the left wall. Approximately 2.5 cm of the extravesical tissue was affected with no signs of metastasis (Fig. 1a). The biopsy showed that the tumor invaded in detrusor muscle, with no evidence of CIS, LVI, or variant histology. Immunohistochemical results were consistent with the previous report (Fig. 2a–c). Pathological findings and radiological assessments confirmed cancer recurrence and muscle invasion (T3bN0M0). After a multi-disciplinary treatment (MDT) discussion involving medical oncology, radiation oncology, radiology, and pathology, the patient received combined neoadjuvant therapy consisting of gemcitabine (1000mg d1, d8/q3w), *cis*-platinum (70mg d1/q3w) and pembrolizumab (200mg d1/q3w). In the process, the patient developed an allergic reaction of systematic rash and pruritus. The white blood cell (WBC) and neutrophil counts decreased to 2.7*109/L and 0.86*109/L, respectively. The treatment-related adverse effect (TRAE) was evaluated as Grade 3 by an experienced physician and was successfully managed with careful symptomatic treatment. After two cycles of treatment, an MRI examination was done to assess the effect (Fig. 1b). Though the mass shrunk to 1.7*1.6cm, extravesical invasion was still visible, approximately 1.6cm. Given the patient's strong desire for bladder preservation and pathological findings of strongly positive HER2, we held an MDT discussion to decide whether to maintain the current plan or modify our strategy to include an ADC combined with a PD-1 inhibitor. The patient agreed to receive the treatment of disitamab veditin combined with pembrolizumab and signed the informed consent. Consequently, we adjusted the therapeutic schedule to a combination of 3 cycles of pembrolizumab (200mg d1/q3w) and 4 cycles of disitamab vedotin (2mg/kg d1/q2w). Encouragingly, pelvic CT and MRI, conducted after two cycles of disitamab vedotin treatment, revealed a reduction in abnormal thickness, and the nodule had shrunk to 0.6 × 0.4 cm. The extravesical invasion was no longer visible (Fig. 1c). Therefore, this strategy was continued and finished. While undergoing treatment with disitamab vedotin and pembrolizumab, the patient complained of mild fatigue and nausea. The complete blood account showed WBC 3.33*109/L, neutrophil 1.27*109/L, and hemoglobin 129 g/L. The TRAE was assessed as grade 2 and active systematic treatment was given. On October 8th, 2022, this patient underwent a second TURBT and postoperative pathology returned no tumor remnant (pT0). Subsequently, another MDT discussion was conducted to proceed with bladder-sparing therapy following the patient's preferences.

From 2022 November 24, the patient commenced a course of regular radiotherapy, consisting of 25 sessions with a total dose of 45 Gy in the pelvic area. Additionally, the dose was locally escalated to 60 Gy in the bladder tumor area. The patient also received concurrent cisplatin chemotherapy (70mg d1/q3w) during the treatment. Though myelosuppression was induced (WBC 2.73*109/L, neutrophil 1.61*109/L, TRAE: grade 2), his condition was improved by symptomatic treatment. On 2023 February 6th and 7th, thoracoabdominopelvic CT, pelvic MRI, cystoscopy and urine cytology returned no tumor remnant. This patient recovered well and did not experience any other complications. Afterward, the patient underwent radiology, cystoscopy, and cytology examination every 3 months. No signs of recurrence have been noted and no specific discomfort was complained until August 2023. The overactive bladder syndrome score (OABSS) score was 2, indicating a mild case of overactive bladder (OAB). The patient was satisfied with our treatment and signed the informed consent. The process of treatment is summarized in Fig. 3.

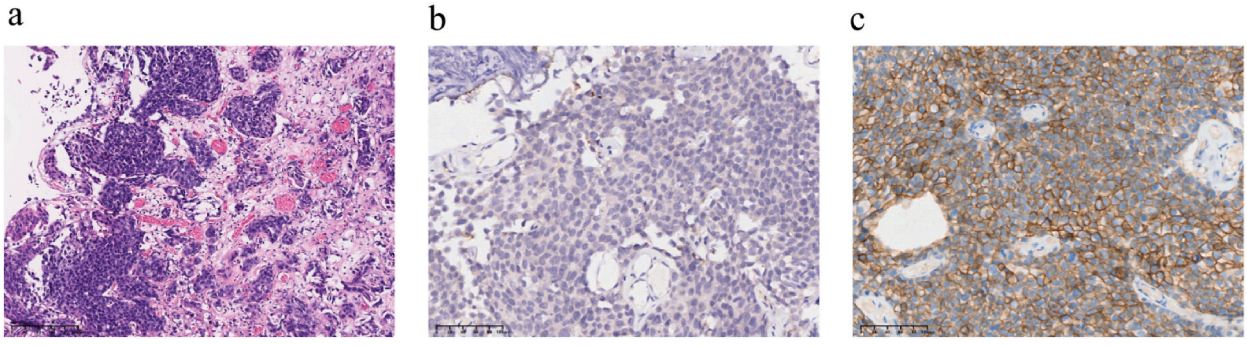

Fig. 2. Biopsy results of the local recurrence. a) The tumor invaded the bladder muscle layer. b) The antibody 22C3 revealed PD-L1 positive. The CPS score was 2. c) The IHC character of HER2 was 3+.

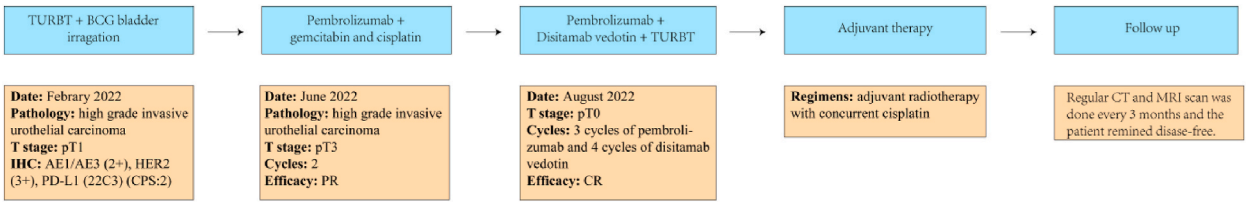

Fig. 3. Important timeline of treatment.

3. Discussion

In this study, we reported a case that underwent neoadjuvant therapy, TURBT, and concurrent chemoradiotherapy, achieving bladder preservation. The neoadjuvant therapy includes pembrolizumab + gemcitabine and cisplatin, as well as pembrolizumab + disitamab vedotin. Though the combination of pembrolizumab and chemotherapy induced tumor shrinkage after two cycles, the extravesical lesion still existed, indicating that downstaging was not achieved. It was possible that continuing the combination of pembrolizumab and chemotherapy may also achieve tumor downstaging. However, the limited efficacy of two consecutive cycles suggested that this was less likely to be the case. Therefore, treating strategy was adjusted after the MDT discussion. The patient achieved a pT0 stage following neoadjuvant treatment with pembrolizumab + disitamab vedotin, and the patient has remained DFS for more than a year. Throughout the entire process, adverse effects ranged from mild to moderate, including fatigue, nausea, and decreased WBC, neutrophil, and hemoglobin. Based on our previous experience with neoadjuvant chemotherapy/neoadjuvant chemotherapy with immunotherapy-guided bladder-sparing therapy of MIBC, bladder preservation is deemed feasible for patients with evident downstaging [2]. In this case, our focus is on the adjustment of neoadjuvant therapy.

Partial cystectomy as a bladder-preserving strategy should also be considered. However, proper indications, including solitary and primary tumors, should be carefully selected [5]. In this case, the locally advanced tumor invaded extravesical tissue. Ensuring a negative surgical margin and a tumor-free surgical process is challenging, increasing the risk of tumor dissemination. Therefore, we opted for radiotherapy to ensure the tumor clearance of extravesical fat tissue and prevent recurrence.

The neoadjuvant therapeutic efficiency in our study was mainly evaluated by MRI. The pathology of TURBT after neoadjuvant therapy was consistent with the MRI results. In massive surgical processes, like maximal TURBT, extensive inflammation, edema, and fibrous generation could be caused, affecting the accuracy of MRI. The MRI vesical imaging - reporting and data system (VI-RADS) consists of T2-weighted (T2W) imaging, DWI, and dynamic contrast-enhanced imaging (DCE MRI). VI-RADS score before and after neoadjuvant immunotherapy of bladder cancer was closely associated with survival and pathological downstaging, indicating that imaging examination is a promising noninvasive assessment [6]. Though VI-RADS showed high accuracy for MIBC, especially tumors in stage T3/T4, it poses challenges in evaluating tumor residual disease after surgery. In our case, though the second biopsy showed muscle invasion, the overall morphology of the tumor was not disrupted as no maximal TURBT was done. Therefore, VI-RADS remained accurate for downstaging evaluation.

Currently, about 21% of patients with high-risk factors in non-muscle invasive bladder cancer (NMIBC) have the potential to progress to MIBC, indicating a worse prognosis [7]. Possible reasons for recurrence include incomplete resection during TURBT, undetected tumors upon cystoscopy, and tumor re-implantation after TURBT [8]. In this case, the primary tumor was NMIBC, but it recurred and invaded the muscle layer after TURBT and intravesical irrigation, indicating a higher malignant potential.

The bladder-sparing tri-modality therapy (TMT) for MIBC has a significant advantage, enhancing the quality of life for patients and demonstrating comparable survival outcomes compared to radical cystectomy [9]. Massachusetts General Hospital reported that TMT for MIBC showed a 5-year survival of 57%. Among them, 66% of patients were at T2 and showed better overall survival rate and disease-specific rates than patients at stage T3/T4a [10]. The current TMT strategy now mainly applied in MIBC of stage T2, where tumors can be effectively eliminated by maximal TURBT. Yet for stages T3/T4, maximal TURBT is not suitable. Once subsequent chemoradiotherapy fails, it may lead to tumor progression or metastasis. Therefore, bladder preservation is only considered possible if obvious downstaging is achieved through neoadjuvant therapy.

At present, several studies are exploring ways to enhance the effectiveness of neoadjuvant therapy and further augment the downstaging rate or pCR. Most of these studies focus on neoadjuvant immunotherapy before radical cystectomy. The downstaging rate of neoadjuvant immunotherapy ranges from 22.5% to 53.5%, which is similar to neoadjuvant chemotherapy [11–13]. While the alliance of immunotherapy and chemotherapy showed superior performance of 56%–60.2% [12,14]. The long-term outcome of neoadjuvant immunotherapy showed that patients with high PD-1 expression exhibited more favorable therapeutic effects. Furthermore, the prognosis of patients with obvious downstaging was better [13].

Evaluation of treatment by radiography after two courses of chemotherapy is an effective way to decide whether to change the treatment strategy. Though the modification of the neoadjuvant therapy scheme has not been extensively studied in MIBC, a few explorations in other tumors have emerged with successful experience. In the context of refractory breast cancer, two reports indicated that second-line neoadjuvant therapy can be administered if the primary treatment showed a limited effect after 3 or 4 cycles. This approach could lead to better tumor control [15,16]. These findings suggest that active adjustment of neoadjuvant therapeutic strategy can be implemented when the initial response is less than ideal.

Clinical research on disitamab vedotin in China has demonstrated promising anti-tumor efficacy. In locally advanced bladder

cancer with HER2 HIC status 2+/3+, combined therapy of disitamab vedotin with PD-1 inhibitors showed an excellent tumor control effect [17]. Nevertheless, disitamab vedotin has not been utilized as neoadjuvant therapy.

Given the success we observed, further exploration of neoadjuvant strategies should be conducted for more pronounced downstaging, such as combining chemotherapy with immunotherapy or ADC drugs with immunotherapy. Furthermore, the specific treatment scheme, particularly the feasibility of adjustments, is worthy of research. For patients with MIBC at T3/T4 stages, the impact of neoadjuvant therapy holds critical guiding significance for bladder preservation.

4. Conclusion

In this report, we emphasize that tumor downstaging serves as a guide for adjusting neoadjuvant therapy regimens. Furthermore, the achievement of tumor downstaging paves the way for bladder-preserving strategies in the management of muscle-invasive bladder cancer. To the best of our knowledge, this is the first attempt at adjustment of neoadjuvant therapy by incorporating pembrolizumab, disitamab vedotin, gemcitabine, and *cis*-platinum in locally advanced bladder cancer, achieving bladder preservation.

Informed consent

Written informed consent was provided by the patient for publishing the information and examination.

Ethics declarations

The patient provided informed consent to participate in the study.

Data availability

The data is included in the article.

CRediT authorship contribution statement

Gan Du: Writing – original draft. **Zhichao Jiang:** Methodology. **Wang Qu:** Methodology. **Jin Zhang:** Investigation. **Shan Zheng:** Resources. **Yueping Liu:** Methodology. **Aiping Zhou:** Investigation. **Hongzhe Shi:** Writing – review & editing. **Jianzhong Shou:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

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.

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