Case Series

ANNALS OF MEDICINE & SURGERY

OPEN

Tislelizumab with gemcitabine and cisplatin as a neoadjuvant regimen for muscle-invasive bladder cancer: case series

Ze Wang, MD[a], Yapeng Wang, MD[a], Shuo Wang, MD[a], Qiang Ran, MD[a], Song Peng, MD[a], Yao Zhang, MD[a], Jun Zhang, MD[a], Dianzheng Zhang, PHD[b], Luofu Wang, PHD, MD[a], Weihua Lan, PHD, MD[a], Qiuli Liu, PHD, MD[a], Jun Jiang, PHD, MD[a,*]

Introduction and importance: The feasibility of combined tislelizumab with gemcitabine and cisplatin as a neoadjuvant regimen for muscle-invasive bladder cancer (MIBC) remains to be investigated.

Case presentation: The neoadjuvant treatment not only shrunk tumours significantly but also lowered their stages from T4bN1M0, T3N0M0, and T3bN0M0 to pT1, pT0 and pTis, respectively. The treatment suppressed tumour cell proliferation and promoted luminal-to-basal transition.

Clinical discussion: MIBC is an aggressive bladder cancer with poor prognosis. All three patients with MIBC benefited greatly from the neoadjuvant regimen (tislelizumab + gemcitabine + cisplatin). It appears that the effect of the treatment is independent of the levels of programmed death-ligand 1 nor the subtype of urothelial bladder cancer.

Conclusion: Combination of tislelizumab with gemcitabine and cisplatin appeared to be a safe and efficacious neoadjuvant therapy for MIBC.

Keywords: case series, muscle-invasive bladder cancer, neoadjuvant therapy, pathological response, tislelizumab

Introduction

Bladder cancer (BCa) is one of the most prevalent cancer types with estimated 81 180 new cases and 17 100 cancer-related deaths in the United States in 2022[1]. Urothelial bladder cancer (UBC) is the most common subtype accounting for 90% BCa. Muscle-invasive bladder cancer (MIBC, stage pT2 or higher) were found in about 30% of patients with UBC upon diagnoses[2]. Due to several factors, mainly the micro-metastasis, patients with MIBC usually have poor prognosis[3,4]. Even with radical cystectomy, about half of MIBC becomes metastatic within 2 years of diagnosis and most patients usually die of cancer[5]. Compared with cystectomy alone, platinum-based neoadjuvant chemotherapy reduced death risk by 16–33% and improved 5–10 year overall survival by 5–6%[6–11] making cisplatin-based neoadjuvant chemotherapy the gold-standard treatment for MIBC[5]. Combination of gemcitabine with cisplatin (GC) has been suggested as a preferred neoadjuvant therapy because of its comparable efficacy to methotrexate, vinblastine, doxorubicin, and cisplatin but lower toxicity[12].

Immune checkpoint inhibitors (ICI) are becoming an attractive therapeutic strategy in the treatment of tumours including metastatic BCa. Compared to chemotherapy alone, combination of ICI with chemotherapy greatly improved prognosis of patients with metastatic UBC who missed the chance for surgical treatment[13]. In addition, multiple clinical trials suggest that combination of ICI with platinum-based chemotherapy could be a new neoadjuvant regimen for patients with advanced tumours

HIGHLIGHTS

- The combination of gemcitabine and cisplatin is a standard neoadjuvant therapy for muscle-invasive bladder cancer (MIBC) patients before radical cystectomy.
- Immune checkpoint inhibitors showed their well therapeutic effects in many types of cancers, including MIBC.
- Tislelizumab with gemcitabine and cisplatin as neoadjuvant therapy could well lower the stages and shrink tumours.
- Minor side-effects were observed for MIBC patients receiving tislelizumab with gemcitabine and cisplatin as neoadjuvant therapy before radical cystectomy.

[a]Department of Urology, Daping Hospital, Army Medical University, Chongqing, China and [b]Department of Bio-Medical Sciences, Philadelphia College of Osteopathic Medicine, Philadelphia, PA

Z.W., Y.W., S.W. contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Urology, Daping Hospital, Army Medical University, at 10#, Changjiang Zhilu, Yuzhong District, Chongqing 400042, PR China. Tel.: +86 023 68757946; fax: +86 023 68757946. E-mail address: jiangjun_64@163.com (J. Jiang).

Annals of Medicine & Surgery (2024) 86:245–251

Received 6 September 2023; Accepted 13 November 2023

Published online 20 November 2023

http://dx.doi.org/10.1097/MS9.0000000000001533

including non-small cell lung cancer, melanoma and oesophageal squamous cell carcinoma[14–16]. By targeting PD-1, the monoclonal IgG4 antibody tislelizumab showed extremely strong effects against Hodgkin's lymphoma, gastric, oesophageal cancer and lung cancer[17]. In China, tislelizumab has been approved for patients with advanced or metastatic urothelial carcinoma who also failed with platinum-based chemotherapy within 12 months (http://drugs.medlive.cn/drugref/html/21697.shtml). Here, we explored the efficacy of tislelizumab combined with gemcitabine and cisplatin as a neoadjuvant treatment for patients with MIBC.

Methods

Patients

Three patients with MIBC were recruited between March, 2022 and July, 2022 and all of them were treated with the neoadjuvant therapy before radical cystectomy. MRI and histopathological analysis were conducted before and after the treatment. All procedures were followed with the ethical standards of the institutional research committee, the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

Neoadjuvant therapy

Tislelizumab (200 mg per vial, Beigene), gemcitabine (200 mg per vial, Eli Lilly and Company) and cisplatin (50 mg per vial, F.H. Faulding Pharmaceuticals Ltd) were dissolved in 0.9% sodium chloride injection (Kelun Pharmaceutical Co., Ltd.). Gemcitabine (1000 mg/m^2) and cisplatin (70 mg/m^2) were administered intravenously on day 1 and gemcitabine (1000 mg/m^2) and tislelizumab (200 mg) on day 8. The treatment timeline is shown in Fig. 1A. Based on previous study[18], patients underwent 2 or 3 cycles of neoadjuvant therapy before radical cystectomy and the side-effects were monitored carefully during the treatment.

Immunohistochemistry (IHC)

Paraffin-embedded tumour tissues were used for IHC[19] with the primary bodies against CK5 (ZA0518, ZSGB-BIO), GATA3 (ZA0661, ZSGB-BIO), Ki67 (ZM0166, ZSGB-BIO) and PD-L1 (SP263, VENTANA). For each specimen, five fields were captured randomly with 400x magnification. Ki67 proliferation index is defined as the ratio between Ki67-positive and total tumour cells. Combined positive score (CPS) is defined as the ratio between PD-L1-positive (tumour cells, lymphocytes, and macrophages) and total tumour cells.

This case series is reported in line with the PROCESS Guideline[20].

Results

Presentation of cases

Patient 1 is a 67-year-old man who was administered to the hospital due to intermittent and painless gross haematuria accompanied by blood colts for 6 months. His haematuria disappeared

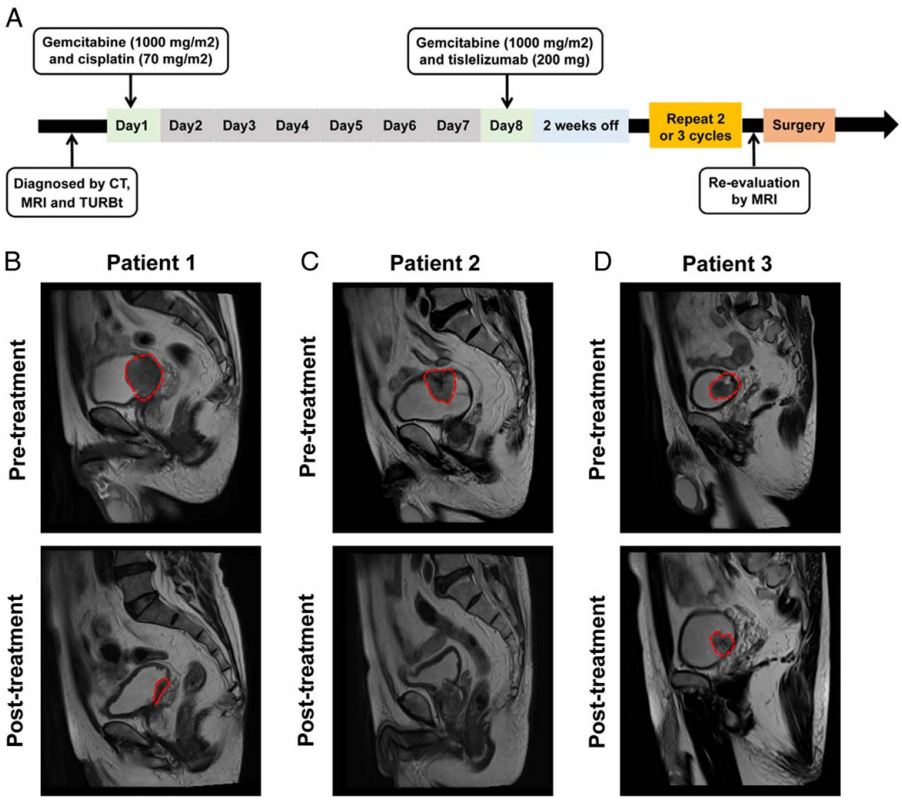

Figure 1. The timeline of patient treatment (A) and the MRI results of patient 1 (B), patient 2 (C) and patient 3 (D) before and after neoadjuvant therapy. CT, computed tomography; TURBt, transurethral resection of bladder tumour.

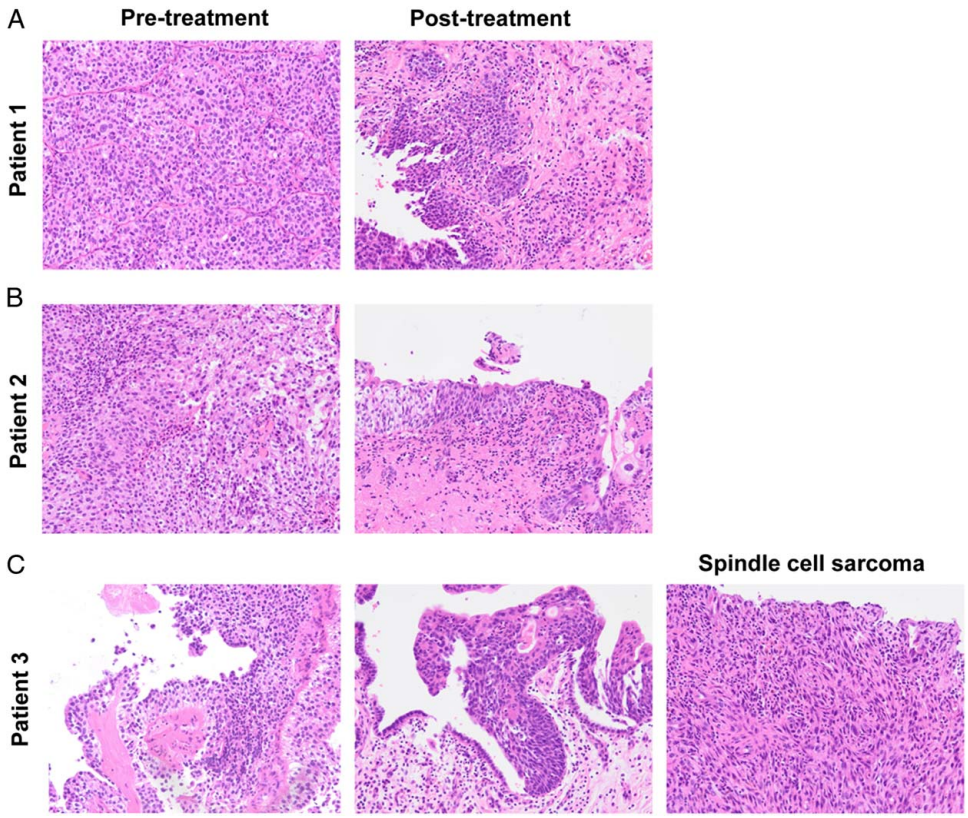

Figure 2. HE staining before and after neoadjuvant therapy of patient 1 (A), patient 2 (B) and patient 3 (C). Original magnification: 200×.

when antibiotics were used initially. He was diagnosed with hypertension 7 years ago with the highest blood pressure of 160/105 mmHg. His hypertension was well controlled (around 110/70 mmHg) with nifedipine (20 mg/day). He also suffered minor renal insufficiency with estimated glomerular filtration rate (eGFR) maintained around 65 ml/min (normal, 90 ml/min). Physical examination did not find any additional abnormality. Renal function test indicated that eGFR was 66.85 ml/min. Pelvic computed tomography (CT) found an irregular mass (4.6 × 6.4 cm) located at the left lateral wall of the bladder with left hydronephrosis and left renal atrophy. Enhanced MRI suggested the tumour as MIBC with invasion to the perivesical fat, left seminal vesicles, and the left paravascular iliac lymph nodes (Fig. 1B). Transurethral resection of bladder tumour (TURBt) indicated that the tumour was high-grade invasive urothelial carcinoma with neuroendocrine differentiation (Fig. 2A), a T4bN1M0 bladder cancer. The patient underwent 3 cycles of neoadjuvant regimen (tislelizumab with gemcitabine and cisplatin). The side-effects included appetite loss with a pain and distend abdomen during treatment. After the neoadjuvant therapy, pelvic MRI showed only limited thickening of bladder wall but the left enlarged paravascular iliac lymph nodes disappeared (Fig. 1B) with negative urine cytology. In the surgically removed sample, only a few cancer cells scattered in mucosa and lamina propria accompanied by fibrous hyperplasia in muscularis propria and inflammatory cells, suggesting his cancer stage lowered to pT1 (Fig. 2A). However, tumour cells were found in the shrunk left paravascular iliac lymph nodes. One year after procedure, the patient developed low back pain. Results from CT scan indicated pulmonary and thoracic metastasis at T12 and lumbar metastasis at L1. Systemic therapy was conducted for the metastases.

Patient 2 is a 73-year-old man with intermittent and painless gross haematuria accompanied by blood clots for 9 months. He also has hypertension but well controlled with amlodipine besylate (5 mg/day). He smokes about 50 pack-year but physical examination was unremarkable. Laboratory work indicated his albumin was 37 g/l (normal, 40–55 g/l). Pelvic CT revealed an irregular mass (4.4 × 2.6 cm) on the left anterior bladder wall, MRI suggested invasion into the muscle layer of bladder (Fig. 1C), and TURBt confirmed that he had high-grade papillary urothelial carcinoma (Fig. 2B). Therefore, his clinical stage was T3M0N0. He underwent three cycles of neoadjuvant therapy before radical cystectomy. He also experienced appetite loss during the therapy. His tumour shrunk to 0.7 × 0.6 cm (Fig. 1C) and the cancer became pT0 evidenced by multifocal dysplasia, stromal fibrous proliferation with glass-like changes and infiltrated lymphocytes but no tumour cell found in the surgical samples (Fig. 2B). No signs of recurrence were found in the subsequent 9 months of follow-up.

Patient 3, a 61-year-old man who smokes 30 pack-year without chronic disease history, presented with painless gross haematuria. He experienced a recurrent and similar symptom accompanied with blood clots 5 months ago but disappeared without any treatment. Both physical and laboratory examinations revealed no abnormities except a reduced level of albumin (39.5 g/l). Pelvic CT revealed multiple intravesical masses in his bladder with the

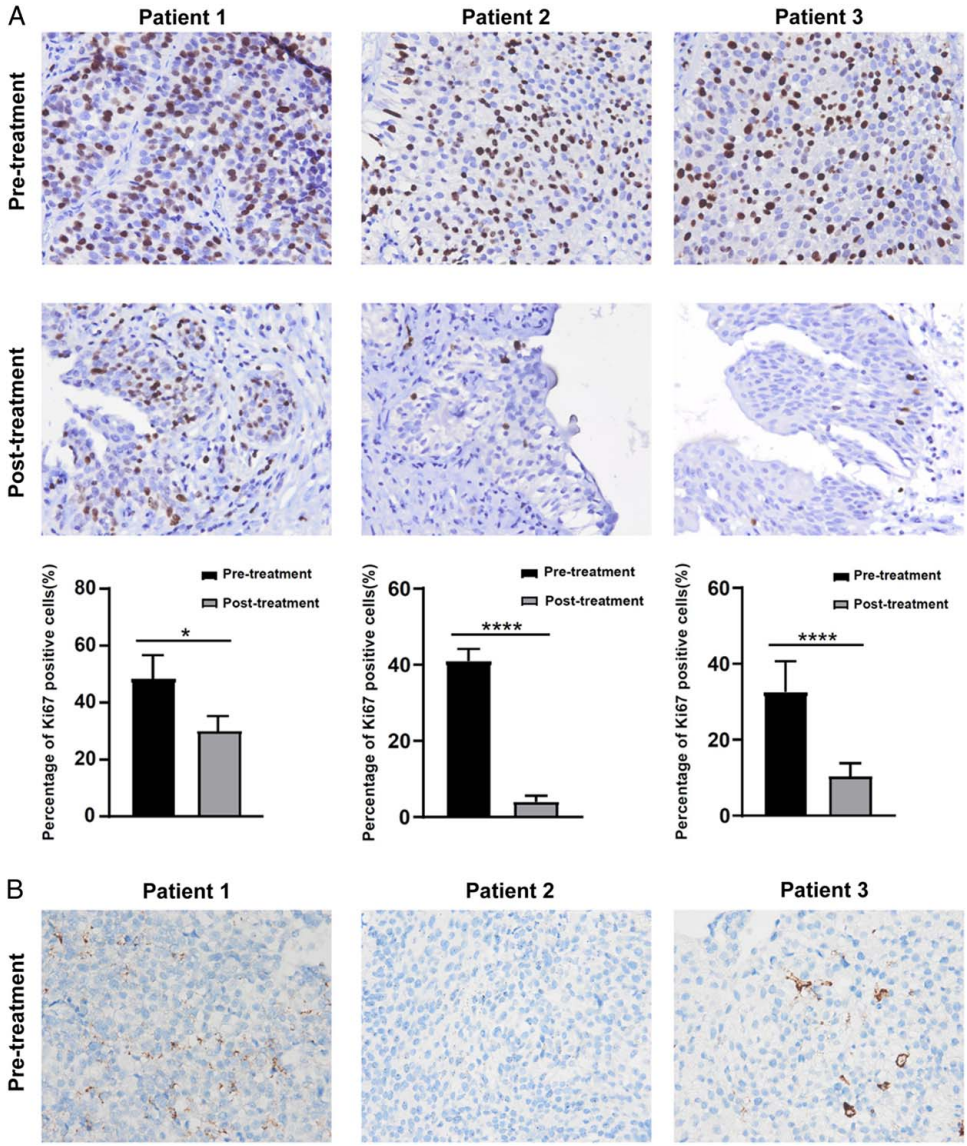

Figure 3. Immunohistochemistry staining for Ki67 of three patients before and after neoadjuvant therapy (A) and PD-L1 before neoadjuvant therapy (B). Original magnification: 400×.

largest one located on the right lateral wall. MRI showed the size of the tumour as 3.3 ×2.2 cm (Fig. 1D) with perivesical fat invasion (T3bN0M0) and TURBt confirmed that the tumour is a high-grade papillary urothelial carcinoma (Fig. 2C). After two cycles of neoadjuvant therapy, the largest tumour shrunk to 1.8 ×1.4 cm (Fig. 1D) and the tumour stage lowered to pTis, because of only carcinoma in situ with spindle cell sarcoma and mucoid degeneration found in specimen (Fig. 2C). The patient showed mild symptoms including fatigue, nausea, and vomiting during the neoadjuvant therapy. During the 7-month follow-up, no sign of either metastasis or recurrence appeared.

The changes in biomarkers

Compared to that of the pretreatment specimens, significantly reduced Ki67-positive cells were seen in all three post-treatment specimens (Patient 1: 48.6% vs. 30.0%, $P=0.016$; Patient 2: 41.0% vs. 4.0%, $P<0.0001$; Patient 3: 32.6% vs. 10.4%, $P<0.0001$) (Fig. 3A) suggesting that tumour cell proliferation was repressed by the therapy. Prior to the treatment, PD-L1 CPS was greater than or equal to 10% and less than 10% in patient 1 and patient 3, respectively, and undetectable in patient 2 (Fig. 3B). We found that the tumour in patient 1 was both GATA3- positive and CK5-positive (Fig. 4A); the tumour in patient 2 was CK5-positive and GATA3-negative (Fig. 4B); and tumour in patient 3 was GATA3-positive and CK5-negative (Fig. 4C). Given that GATA3 and CK5 had been suggested as biomarkers for luminal or basal subtyping[21], these results suggested that the repressive effect of the neoadjuvant therapy depended on neither PD-L1 expression nor UBC subtype. In addition, the levels of GATA3 and CK5 significantly decreased and increased, respectively, after neoadjuvant treatment in patient 1 and patient 3.

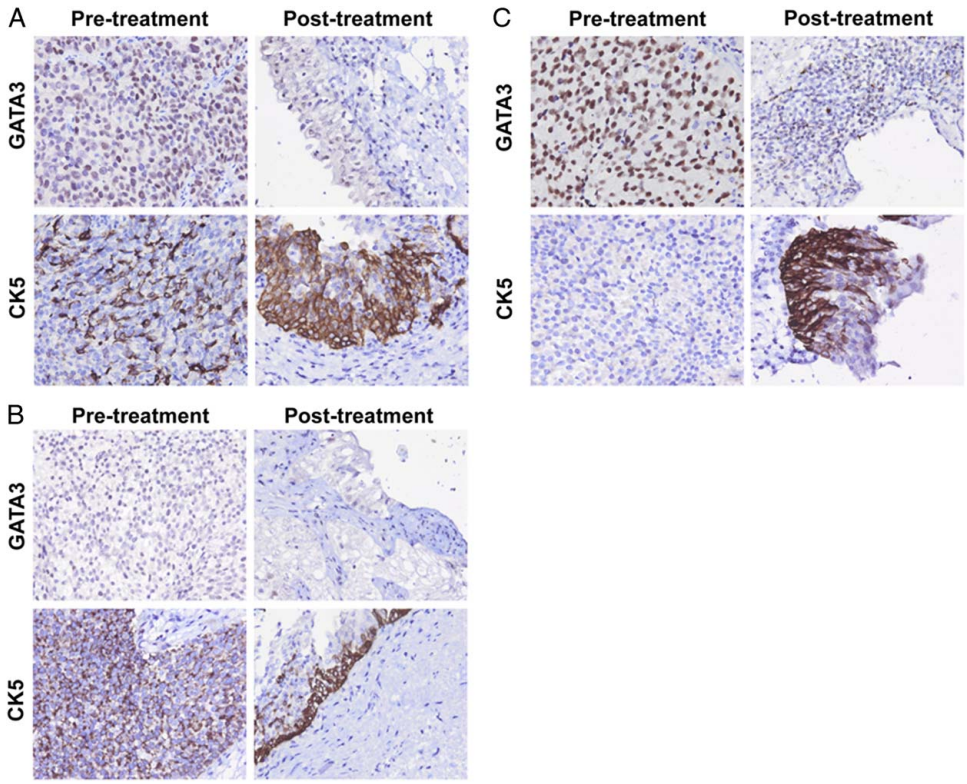

Figure 4. Immunohistochemistry staining for GATA3 and CK5 of patient 1 (A), patient 2 (B) and patient 3 (C) before and after neoadjuvant therapy. Original magnification: 400×.

Discussion

We explored the effect of a potential new neoadjuvant regimen on MIBC and found that the tumours in all three patients treated with the regimen shrunk significantly and the tumour stages lowered from T4bN1M0, T3N0M0, and T3bN0M0 to pT1, pT0, and pTis, respectively. The treatment repressed tumour cell proliferation and promoted luminal-to-basal transition. In addition, it appears that the effect of the regimen depended on neither PD-L1 expression nor UBC subtype. Since all three patients manifested with minor adverse effect, this regimen could be developed into an alternative neoadjuvant therapy for MIBC.

All patients undergoing the new therapeutic treatment suffered gross haematuria, which should be differentiated from urinary stones, inflammation and the upper tract urothelial carcinoma. Patients with urinary stones usually had back or abdominal pain. Patients with urinary inflammation usually showed urinary urgency, frequent and painful urination with increased urinary white cells. However, all three patients in this study presented with painless gross haematuria accompanied by blood clots, a typical symptom of urothelial tumour. Additionally, both enhanced CT and MRI suggested that tumours were localized to the bladder lumen rather than the upper tract and TURBt finally confirmed that these were urothelial tumour. Notably, clinical diagnosis of MIBC was usually based on CT and MRI because the TURBt specimens were barely detected with muscular layer[22].

The positive effects of ICI as neoadjuvant regimen on various tumours have been reported. The use of cabozantinib and nivolumab as neoadjuvant therapy for advanced hepatocellular carcinoma led to 80–100% pathologic clinical response (pCR, pT0N0)[23]. Weber *et al.*[24] reported that neoadjuvant ipilimumab and nivolumab in patients with stage III melanoma achieved 77% pCR rate with 20% of them showing a grade 3/4 adverse reactions. For BCa, pembrolizumab alone as a neoadjuvant regimen achieved 54% pCR rate[25]. Neoadjuvant atezolizumab in MIBC was associated with pCR rate of 31% and long progression-free survival[26]. In line with these reports, we found that combination of ICI tislelizumab with GC also lowered tumour T stage in UBC patients.

In China, tislelizumab has been approved as a second-line chemotherapy for patients with relapsed or refractory classical Hodgkin's lymphoma[17]. Clinical trials indicated tislelizumab possessed anti-tumour effects in urothelial carcinoma[17]. When tislelizumab was used in patients with PD-L1-positive urothelial carcinoma, objective response rate (ORR), complete response, and partial response rate were 23%, 8%, and 15%, respectively[27]. The ORR in an open-label, phase I/II trail of urothelial carcinoma achieved 14% (3/22 patients)[28]. When it was used in patients with previously-treated urothelial carcinoma, the ORR reached 29.4% (5/17)[29]. As multiple clinical trials (ChiCTR2000037670, ChiCTR2200061816, NCT04813107, and NCT05328336) combining tislelizumab with different chemotherapies as neoadjuvant regimens for MIBC are ongoing, it is unsurprised by the encouraging results when tislelizumab is combined with GC as an alternative neoadjuvant treatment of MIBC. Notably, the efficacy of immunotherapy was associated with both age and sex[30,31]. Since all three patients in our study were elderly male, further studies with variously aged patients are needed.

Similar to that of the combination of pembrolizumab with GC[32], it appeared that the effect of our regimen was irrelevant to the levels of PD-L1. It has been noticed that loss of GATA3 promotes bladder cancer migration and invasion[33] and low-GATA3/high-CK5 predicts poor prognosis of MIBC[34]. Although our regimen increased and decreased tumour CK5 and GATA3, respectively, suggesting a luminal-to-basal transition, studies with larger sample size are needed. In addition, Ki67 expression appeared to be associated with UBC aggressiveness evidenced by higher grade, muscle invasion, and increased post-operative circulating tumour cells[35,36]. All three patients in our study had relatively high levels of Ki67 and all responded well to the treatment, suggesting the levels of Ki67 might be an indicator of responsiveness. In addition, significant reduction of Ki67 levels further supported the anti-tumour effect of the regimen. Although the outcome is encouraging, given the limited number of patients in this study, solid conclusions will only be obtained from studies with larger sample size.

Conclusion

Combination of tislelizumab with gemcitabine and cisplatin shrunk tumours significantly in all three patients and the tumour stages lowered from T4bN1M0, T3N0M0, and T3bN0M0 to pT1, pT0 and pTis, respectively, accompanied by reduced tumour cell proliferation. The effect of the regimen appeared to be independent of PD-L1 expression nor UBC subtype. Since all patients manifested very minor adverse effect, the regimen possesses great potential to be developed as a safe and effect adjuvant therapy.

Ethical approval

This study was approved by the ethics committee of Daping hospital (2011-163).

Consent

Written informed consent was obtained from the patients for the publication of this case report with accompanying images. A copy of the written informed consent is available for review by the Editor-in-Chief on request.

Sources of funding

This work was supported by the National Natural Science Foundation of China (Grant No: 82172721 and 82172807); University Research Project of Army Medical University (2021XQN24, 2018XLC1014 and 2019CXLCB006). The sponsors had no above-mentioned involvement.

Author contribution

J.J. and Q.L. designed the study. Z.W., Y.W. and S.W. performed the experiments. Z.W., Q.R., and S.P. collected the clinical data. The data were analyzed by Z.W., Y.W. and S.W. Y.Z., J.Z., L.W. and W.L. contributed to patient enrolment and sample collection. Q.L., Z.W. and D.Z. drafted the manuscript. J.J. and Q.L. were responsible for arrangement and supervision. All authors contributed to the article and approved the submitted version.

Conflicts of interest disclosure

The authors declare no potential conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Jun Jiang had full responsibility for the work, the conduct of the study and data access and controlled the decision to publish.

Data availability statement

The data generated in this study were available on request.

Provenance and peer review

Not invited.

Acknowledgements

The authors thank all patients in this study for their collaboration. The authors also thank Drs. Qiang Ma and Peng Zhong from the Department of Pathology, Daping hospital for their assistance in analyzing tissue samples.

References

[1] Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
[2] D Brierley J, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 8th edn; 2016.
[3] Bamias A, Merseburger A, Loriot Y, *et al*. New prognostic model in patients with advanced urothelial carcinoma treated with second-line immune checkpoint inhibitors. J Immunother Cancer 2023;11:e005977.
[4] Mohamed HI, Aly M, Badran Y, *et al*. Recent advances in three-dimensional ultrasound virtual cystoscopy in modeling and local staging for urothelial carcinoma with histopathological correlation; a cohort prospective study. Ann Med Surg (Lond) 2023;85:5365–71.
[5] Witjes JA, Bruins HM, Cathomas R, *et al*. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol 2021;79:82–104.
[6] Grossman HB, Natale RB, Tangen CM, *et al*. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
[7] Griffiths G, Hall R, Sylvester R, *et al*. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011;29:2171–7.
[8] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003;361:1927–34.
[9] Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48:202–5; discussion 205-206.
[10] Iyer G, Balar AV, Milowsky MI, *et al*. Multicenter prospective phase II trial of neoadjuvant dose-dense gemcitabine plus cisplatin in patients with muscle-invasive bladder cancer. J Clin Oncol 2018;36:1949–56.
[11] Peyton CC, Tang D, Reich RR, *et al*. Downstaging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. JAMA Oncol 2018;4:1535–42.

[12] Roberts JT, von der Maase H, Sengeløv L, *et al*. Long-term survival results of a randomized trial comparing gemcitabine/cisplatin and methotrexate/vinblastine/doxorubicin/cisplatin in patients with locally advanced and metastatic bladder cancer. Ann Oncol 2006;17(Suppl 5):v118–22.
[13] Feng Z, Vuky J. Combination therapy with immune checkpoint inhibitors in urothelial carcinoma: current data and future outlook. Oncology (Williston Park) 2021;35:410–20.
[14] Forde PM, Spicer J, Lu S, *et al*. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 2022;386:1973–85.
[15] Rozeman EA, Hoefsmit EP, Reijers ILM, *et al*. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma. Nat Med 2021;27:256–63.
[16] Yin J, Yuan J, Li Y, *et al*. Neoadjuvant adebrelimab in locally advanced resectable esophageal squamous cell carcinoma: a phase 1b trial. Nat Med 2023;29:2068–78.
[17] Lee A, Keam SJ. Tislelizumab: First Approval. Drugs 2020;80:617–24.
[18] Chen H, Yang W, Xue X, *et al*. Neoadjuvant immunotherapy and chemoimmunotherapy for stage II-III muscle invasive bladder cancer. Front Immunol 2022;13:986359.
[19] Liu Q, Tong D, Liu G, *et al*. Metformin inhibits prostate cancer progression by targeting tumor-associated inflammatory infiltration. Clin Cancer Res 2018;24:5622–34.
[20] Agha RA, Sohrabi C, Mathew G, *et al*. The PROCESS 2020 Guideline: Updating Consensus Preferred Reporting Of CasESeries in Surgery (PROCESS) Guidelines. Int J Surg 2020;84:231–5.
[21] Guo CC, Bondaruk J, Yao H, *et al*. Assessment of luminal and basal phenotypes in bladder cancer. Sci Rep 2020;10:9743.
[22] Chamie K, Ballon-Landa E, Bassett JC, *et al*. Quality of diagnostic staging in patients with bladder cancer: a process-outcomes link. Cancer 2015;121:379–85.
[23] Ho WJ, Sharma G, Zhu Q, *et al*. Integrated immunological analysis of a successful conversion of locally advanced hepatocellular carcinoma to resectability with neoadjuvant therapy. J Immunother Cancer 2020;8:e000932.
[24] Weber J, Glutsch V, Geissinger E, *et al*. Neoadjuvant immunotherapy with combined ipilimumab and nivolumab in patients with melanoma with primary or in transit disease. Br J Dermatol 2020;183:559–63.
[25] Necchi A, Anichini A, Raggi D, *et al*. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol 2018;36:3353–60.
[26] Szabados B, Kockx M, Assaf ZJ, *et al*. Final results of neoadjuvant atezolizumab in cisplatin-ineligible patients with muscle-invasive urothelial cancer of the bladder. Eur Urol 2022;82:212–22.
[27] Ye D, Liu J, Zhou A, *et al*. First report of efficacy and safety from a phase II trial of tislelizumab, an anti-PD-1 antibody, for the treatment of PD-L1 + locally advanced or metastatic urothelial carcinoma (UC) in Asian patients. Ann Oncol 2019;30:v367.
[28] Shen L, Guo J, Zhang Q, *et al*. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer 2020;8:e000437.
[29] Desai J, Deva S, Lee JS, *et al*. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J Immunother Cancer 2020;8:e000453.
[30] Chong PP, Rubin JB, Abdullah M, *et al*. Editorial: differential efficacy of immune checkpoint inhibitors due to age and sex factors. Front Immunol 2022;13:941254.
[31] Lin A, Zhang H, Hu X, *et al*. Age, sex, and specific gene mutations affect the effects of immune checkpoint inhibitors in colorectal cancer. Pharmacol Res 2020;159:105028.
[32] Rose TL, Harrison MR, Deal AM, *et al*. Phase II study of gemcitabine and split-dose cisplatin plus pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive bladder cancer. J Clin Oncol 2021;39:3140–8.
[33] Li Y, Ishiguro H, Kawahara T, *et al*. Loss of GATA3 in bladder cancer promotes cell migration and invasion. Cancer Biol Ther 2014;15:428–35.
[34] Jangir H, Nambirajan A, Seth A, *et al*. Prognostic stratification of muscle invasive urothelial carcinomas using limited immunohistochemical panel of Gata3 and cytokeratins 5/6, 14 and 20. Ann Diagn Pathol 2019;43:151397.
[35] Liu J, Ma C, Li X, *et al*. Circulating tumor cells correlating with Ki-67 predicts the prognosis of bladder cancer patients. Int Urol Nephrol 2023,55:309–18.
[36] Hasan A, Mohammed Y, Basiony M, *et al*. Clinico-pathological features and immunohistochemical comparison of p16, p53, and Ki-67 expression in muscle-invasive and non-muscle-invasive conventional urothelial bladder carcinoma. Clin Pract 2023;13:806–19.