

Complete Response To Tislelizumab In A Muscle-Invasive Urothelial Carcinoma After Surgery Associated With Tumor Mutational Burden High: A Case Report

Jing Jin

Department of Urology, Shaoxing People's Hospital

Qidong Yang

The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd

Yangyang Yu

The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd

Lin Chen

The Medical Department, Jiangsu Simcere Diagnostics Co., Ltd

Shouhua Pan (✉ 13606550587@163.com)

Department of Urology, Shaoxing People's Hospital

Research Article

Keywords: Muscle-invasive urothelial carcinoma, tislelizumab, adjuvant treatment, TMB-H, complete response

Posted Date: January 14th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1226643/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Muscle-invasive urothelial carcinoma (MIUC) is a highly aggressive urothelial carcinoma. Radical cystectomy (RC) is standard of treatment, but still more than 50% patients with cancer invading the muscularis propria or involving the regional lymph nodes will have metastatic recurrence. In CheckMate274 study, programmed cell death-1 (PD-1) inhibitor nivolumab as adjuvant treatment has shown effective for patients with MIUC. Tislelizumab is an anti-human PD-1 monoclonal IgG4 antibody which was specifically engineered to minimize Fc γ R macrophage binding to abrogate antibody-dependent phagocytosis. But there is no report of tislelizumab as adjuvant treatment in MIUC currently. Here, we report a case of MIUC in a patient with PD-L1-negative, microsatellite stable (MSS), high tumor mutational burden (TMB-H) obtained complete response (CR) receiving tislelizumab therapy after surgery. Progression-free survival (PFS) exceeded 6 months since tislelizumab treatment. To our knowledge, this is the first reported case of MIUC patient with PD-L1-negative, MSS and TMB-H who responded well to tislelizumab as adjuvant treatment. However, we still need more studies to assess the efficacy of tislelizumab as adjuvant treatment in MIUC and to confirm that TMB is a predicted biomarker of tislelizumab for efficacy.

Short Report

Urothelial carcinoma (UC) is the most common tumor of genitourinary malignancy with considerable mortality in the world [1]. Muscle-invasive urothelial carcinoma (MIUC) is a highly aggressive UC. Radical cystectomy (RC) is standard of treatment, but still more than 50% of patients with cancer invading the muscularis propria or involving the regional lymph nodes will have metastatic recurrence [2]. The CheckMate274 study shows that patients with PD-L1 \geq 1% of high-risk primary invasive UC can benefit from the adjuvant treatment of programmed cell death-1 (PD-1) inhibitor nivolumab [3]. Tislelizumab is an anti-human PD-1 monoclonal IgG4 antibody which was specifically engineered to minimize Fc γ R macrophage binding to abrogate antibody-dependent phagocytosis [4]. And tislelizumab has been approved in China to treat patients locally advanced or metastatic UC. But there is no report of tislelizumab as adjuvant treatment in MIUC currently. Here, we report a case of MIUC with PD-L1-negative, microsatellite stable (MSS), high tumor mutational burden (TMB-H) obtained complete response (CR) receiving tislelizumab therapy after surgery.

A 73-year-old male presented to our hospital with gross hematuria for more than one year in December 2020. Diffusion-weighted imaging (DWI) was performed and revealed occupying lesion in the left ureter with fluid, thickening of the wall of the bladder. The initial clinical diagnosis was bladder tumor. The patient underwent transurethral resection of bladder tumor and was diagnosed with MIUC. Subsequently, computed tomography urography (CTU) revealed occupation in the wall of the middle and lower section of the left ureter and multiple enlarged lymph nodes distributed in the pelvis, around the abdominal aorta and in retroperitoneum. Laparoscopic radical cystectomy and pelvic lymphadenectomy were performed, but retroperitoneal lymph nodes could not be completely removed. Postoperational immunohistochemical staining (IHC) of bladder biopsy showed CD31 (+) on vascular endothelial cells,

CEA (-), CK20 (+), CK7 (+), Ki-67 (+30%), P53 (+), P63 (+), GATA-3 (+), CD10 (partial +) (fig1). Finally, the disease was diagnosed as stage IV MIUC (T4bN3M1) (fig2).

The patient refused chemotherapy due to poor physical conditions. As an alternative, precise treatment was considered, PD-L1 IHC assay (SP263) and a pan-panel 539 genes next-generation sequencing (NGS) analysis was performed on formalin-fixed and paraffin-embedded specimens and white blood cell. The status of microsatellite instability (MSI) was evaluated as MSS based on NGS, and TMB was calculated to be 21.28 Muts/Mb and evaluated as TMB-H. Meanwhile, 37 somatic genetic mutations (Supplementary Table S1) and 6 germline mutations (Supplementary Table S2) were found in tumor sample. PD-L1 protein expression was negative (TC \leq 1%) based on the SP263-IHC assay (fig1). The patient received tislelizumab therapy (200 mg on D1, every 3 weeks) as adjuvant treatment in April 2021. After 4 months, the residual lesions attained complete remission (fig3). Progression-free survival (PFS) exceeded 6 months since tislelizumab treatment.

In NCT04004221/CTR20170071 study, tislelizumab has shown antitumor activity in patients with previously treated metastatic PD-L1 -positive UC with 24% ORR as second-line treatment [5]. Based on the data of this research, tislelizumab had been approved in China to treat patients with high PD-L1 expression with locally advanced or metastatic UC who have failed platinum containing chemotherapy. However, the efficacy of tislelizumab as a postoperative adjuvant treatment in MIUC has not yet been reported. In our case, the residual lesions obtained CR after receiving tislelizumab as adjuvant treatment, and PFS lasted for 6 months. This shows that tislelizumab is effective in the adjuvant treatment of MIUC.

NCT04004221/CTR20170071 study results had shown that treatment-experienced patients with PD-L1-positive UC can benefit from tislelizumab [5]. However, clinical benefit from tislelizumab was only observed in patients with PD-L1-negative UC with 18% ORR in CTR20160872 study [6]. Only 4 UC patients with PD-L1-positive were enrolled to this trial may be the reason for this phenomenon. This also indicates that UC patients with PD-L1-negative can benefit from tislelizumab. Besides PD-L1 expression, MSI and TMB have also been regarded as a predictive biomarker of immunotherapy response. Our patient was PD-L1-negative, MSS and only TMB-H. Residual lesions attained complete remission after tislelizumab treatment. This indicates that tislelizumab might be a promising treatment option for MIUC patients with PD-L1-negative, MSS and TMB-H.

To our knowledge, this is the first reported case of MIUC patient with PD-L1-negative, MSS and TMB-H who responded well to tislelizumab as adjuvant treatment. However, we still need more studies to assess the efficacy of tislelizumab as adjuvant treatment in MIUC and to confirm that TMB is a predicted biomarker for efficacy.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent was obtained from the patient.

Availability of data and materials

Not applicable.

Competing Interests

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Conception/Design: Shouhua Pan, Jing Jin. Provision of study material or patients: Jing Jin, Qidong Yang, Yangyang Yu. Collection of data: Jing Jin. Data analysis and interpretation: Qidong Yang. Manuscript writing: Jing Jin, Qidong Yang, Yangyang Yu, Lin Chen. Final approval of manuscript: Shouhua Pan.

Acknowledgment

We thank Mingzhe Xiao and Chuang Qi from Jiangsu Simcere Diagnostics for his kindly assistance.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

Not applicable.

Informed consent

Informed consent was obtained from the patient.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6):394–424. doi:10.3322/caac.21492
2. Stein JP, Lieskovsky G, Cote R et al (2001) Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. *J Clin Oncol* 19(3):666–675. doi:10.1200/JCO.2001.19.3.666
3. Bajorin DF, Witjes JA, Gschwend JE et al (2021) Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med* 384(22):2102–2114. doi:10.1056/nejmoa2034442
4. Lee A, Keam SJ, Tislelizumab (2020) First Approval *Drugs* 80(6):617–624. doi:10.1007/s40265-020-01286-z
5. Ye D, Liu J, Zhou A et al (2021) Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. *Cancer Sci* 112(1):305–313. doi:10.1111/cas.14681
6. Shen L, Guo J, Zhang Q et al (2020) Tislelizumab in Chinese patients with advanced solid tumors: An open-label, non-comparative, phase 1/2 study. *J Immunother Cancer* 8(1). doi:10.1136/jitc-2019-000437

Figures

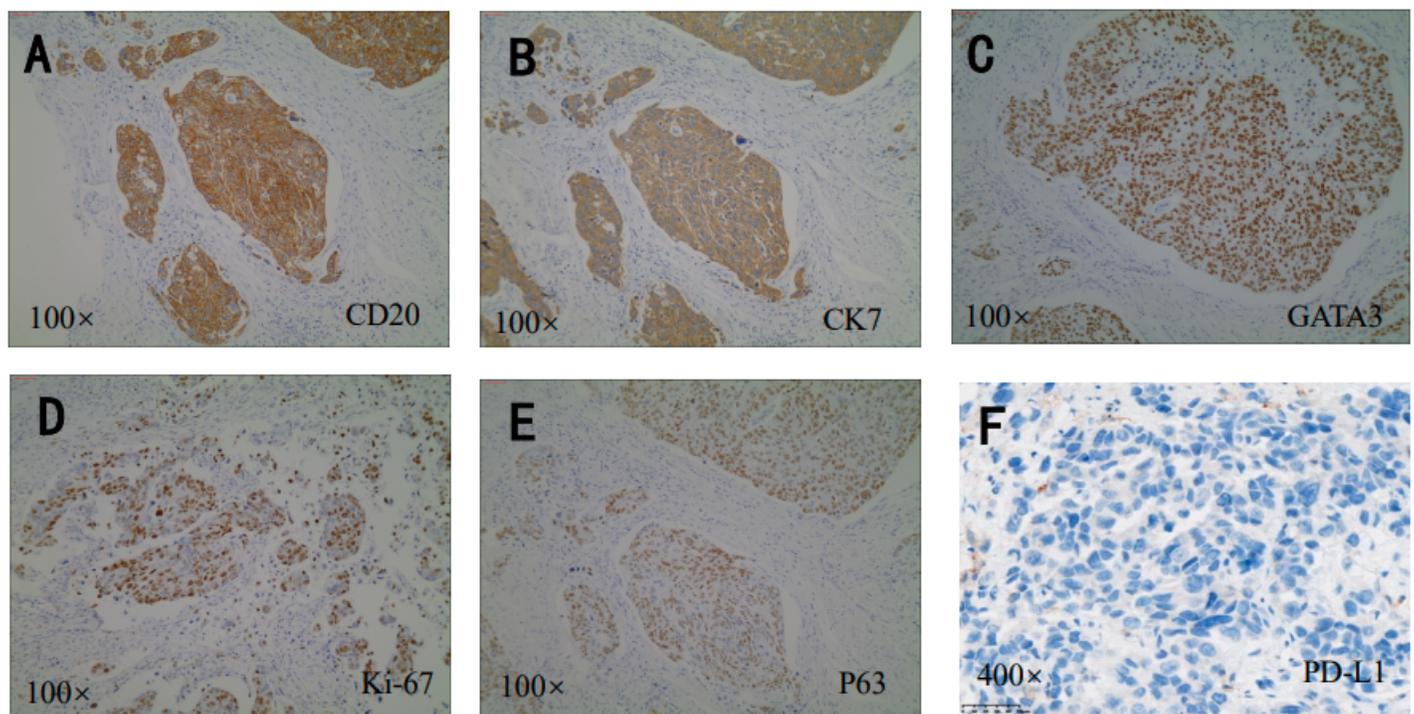


Figure 1

Histopathologic stains from the bladder biopsy (A) CD20; (B) CK7; (C) GATA3; (D)Ki-67 (E)P63; (F)PD-L1 expression.

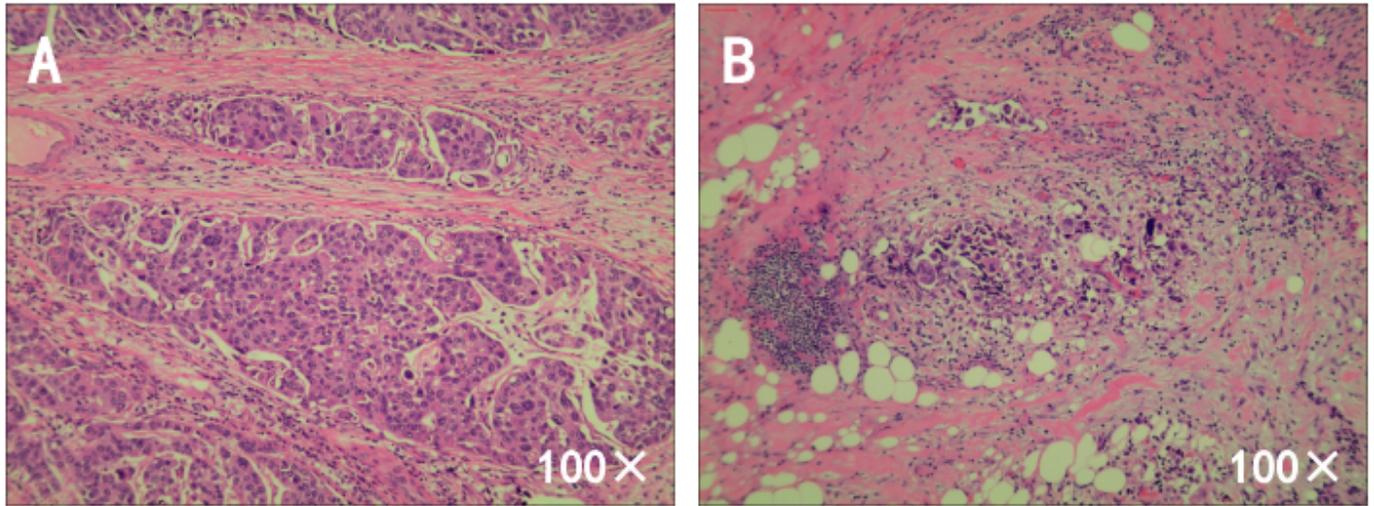


Figure 2

Hematoxylin and eosin (HE) staining of biopsy tumor tissue. (A) Bladder tissue; (B)Peritoneal nodule.

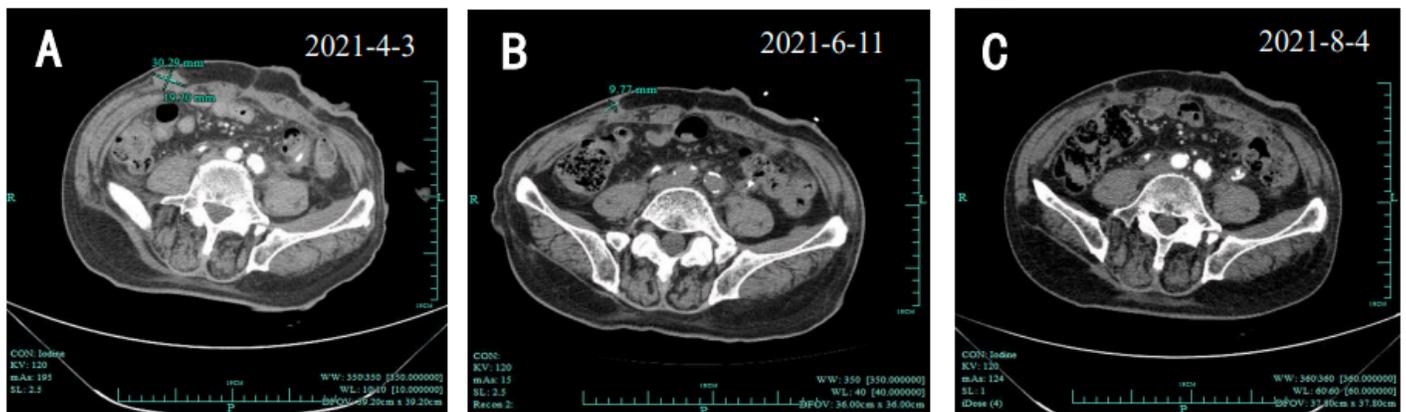


Figure 3

Tumor response during tislelizumab treatment. (A) Baseline before tislelizumab treatment; (B) 2 month after tislelizumab treatment (C) 4 months after tislelizumab treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTableS1.docx](#)

- [SupplementaryTableS2.docx](#)