

81344\_Auto\_Edited.docx

**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 81344

**Manuscript Type:** CASE REPORT

**Bladder preservation in complicated invasive urothelial carcinoma following treatment with cisplatin/gemcitabine plus tislelizumab: A case report**

Bladder preservation in invasive urothelial carcinoma

Rui Yang, Jun-Xing Chen, Shu-Hang Luo, Ting-Ting Chen, Ling-Wu Chen, Bin Huang

## **Abstract**

### **BACKGROUND**

Invasive urothelial carcinoma with squamous and glandular differentiation is a highly malignant and complicated pathological subtype, and the standard care is radical cystectomy. However, urinary diversion after radical cystectomy significantly reduces patient quality of life, thus bladder-sparing therapy has become a research hotspot in this field. Recently, five immune checkpoint inhibitors have been approved for systemic therapy of locally advanced or metastatic bladder cancer by the Food and Drug Administration, but the efficacy of immunotherapy combined with chemotherapy for invasive urothelial carcinoma is still unknown, especially for pathological subtypes with squamous and glandular differentiation.

### **CASE SUMMARY**

We report the case of a 60-year-old male who complained of repetitive painless gross hematuria and was diagnosed with muscle-invasive bladder cancer with squamous and glandular differentiation, defined as cT3N1M0 according to the American Joint Committee on Cancer, who had a strong desire to preserve the bladder. Immunohistochemical staining revealed that programmed cell death-ligand 1 (PD-L1) expression in the tumor was positive. Thus, a transurethral resection to maximize removal of the bladder tumor was performed under cystoscopy, and the patient subsequently received a combination of chemotherapy (cisplatin/gemcitabine) and immunotherapy (tislelizumab) treatment. No tumor recurrence in the bladder was observed following pathological and imaging examination after 2 cycles and 4 cycles of treatment, respectively. The patient achieved bladder preservation and has been tumor-free for more than two years.

### **CONCLUSION**

This case shows that the combination of chemotherapy and immunotherapy might be an effective and safe treatment strategy for PD-L1 expression positive urothelial carcinoma with divergent histologic differentiation.

**Key Words:** Invasive urothelial carcinoma; Immunotherapy; Chemotherapy; Squamous and glandular differentiation; Tislelizumab; Case report

Yang R, Chen JX, Luo SH, Chen TT, Chen LW, Huang B. Bladder preservation in complicated invasive urothelial carcinoma following treatment with cisplatin/gemcitabine plus tislelizumab: A case report. *World J Clin Cases* 2022; In press

**Core Tip:** Urothelial carcinoma with complicated differentiation is highly malignant, and radical cystectomy (RC) is the preferred treatment. Because of the complications related to RC, bladder-sparing therapy has become a research hotspot. We here report a patient who was diagnosed with muscle-invasive bladder cancer with squamous and glandular differentiation and positive programmed cell death-ligand 1 (PD-L1) expression. The patient received a combination of chemotherapy and immunotherapy and achieved bladder preservation and has maintained tumor-free for over two years. This case highlights that the combination treatment might be an effective and safe strategy for urothelial carcinoma with divergent histologic differentiation and positive PD-L1 expression.

## **INTRODUCTION**

Urothelial carcinoma (UC), originating in the bladder or upper urinary tract, is the most common histological type of cancer<sup>[1]</sup>. UC has a wide range of clinical and morphological characteristics, including the unique ability to differentiate into all histological variants, including squamous, glandular, micropapillary, sarcomatoid, small cell, clear cell and so on<sup>[2]</sup>. The biological behavior and treatment strategy of a bladder tumor with variant histology differs from that of conventional UC, which is an

uncertain and difficult challenge for clinicians<sup>[3]</sup>. Although radical cystectomy (RC) is the preferred standard treatment for muscle-invasive bladder cancer (MIBC) according to the National Comprehensive Cancer Network (NCCN), some patients still have a strong desire to preserve the bladder due to the marked decline in quality of life after RC. Unfortunately, effective bladder-sparing treatments are limited.

<sup>2</sup>Platinum-based cytotoxic chemotherapy is the standard treatment for metastatic or locally advanced UC and the preferred treatment option in the perioperative (neoadjuvant and/or adjuvant) setting for MIBC. However, the overall significance of the mixed histological features of MIBC remains unclear. In addition, with the <sup>2</sup>increased understanding of cancer immunobiology, systematic immunotherapy targeting immune checkpoint suppression has been explored and clinically applied in the field of UC<sup>[4]</sup>.

Herein, we report a case of programmed cell death-ligand 1 (PD-L1) expression positive MIBC with squamous and glandular differentiation, who refused total cystectomy. The patient received combination treatment with chemotherapy and immunotherapy after successful transurethral resection of the bladder tumor (TURBT). A marked response to combination treatment was achieved and the patient successfully preserved bladder function.

## **CASE PRESENTATION**

### ***Chief complaints***

In August 2020, a 60-year-old male patient was admitted to <sup>10</sup>the Department of Urology of The First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, China) with repetitive painless gross hematuria and a 6-mo history of blood clots.

### <sup>1</sup>***History of present illness***

None

### ***History of past illness***

The patient had no history of chronic respiratory, cardiovascular or other medical conditions.

### *Personal and family history*

There was no history of genetic disease or UC in his family.

1

### *Physical examination*

On admission, the patient's temperature was 36.6°C, heart rate was 70 bpm, respiratory rate was 15 breaths/min, and blood pressure was 136/83 mmHg. The abdomen was soft without masses or organomegaly, and no tenderness or percussed pain was observed at lower abdomen.

### *Laboratory examinations*

Routine blood tests revealed red blood cell, white blood cell, and platelet counts of  $4.75 \times 10^{12}/L$ ,  $7.47 \times 10^9/L$ , and  $229 \times 10^9/L$ , respectively, and hemoglobin level of 147 g/L. Prothrombin and partial thromboplastin times were normal, but the level of fibrinogen was 4.82 g/L (2.00 - 4.00 g/L). The results of blood biochemistry tests were within normal ranges. Serum creatinine level was 78  $\mu\text{mol}/L$  and blood urea nitrogen level was 3.9 mmol/L, indicating normal renal function. Routine urine test revealed higher amounts of protein, red blood cells and white blood cells in urine. The electrocardiography and chest X-ray were normal.

### *Imaging examinations*

Pelvic MRI revealed a 24×42×29 mm mass located at the posterior wall of the bladder, which invaded the entire muscular layer and the serosa (Figure 1A). Suspicious enlarged lymph nodes adjacent to the left internal iliac vessels in the pelvic cavity were observed (Figure 1E). Cystoscopy and diagnostic TURBT were performed for further examination. Cystoscopy revealed a mass (approximately 45 mm in diameter) at the posterior wall of the bladder, with necrotic tissue and blood clots on the surface (Figure

2A). Pathological examination revealed high-grade invasive UC with squamous and adenoid differentiation (Figure 3A and 3B), and immunohistochemistry results showed positive expression of some intestinal adenocarcinoma markers. Based on the imaging, pathological and other examinations, the patient was staged as cT3N1M0 according to the American Joint Committee on Cancer.

### **FINAL DIAGNOSIS**

The patient was preliminarily diagnosed with MIBC, whose pathological type was complicated UC with squamous and glandular differentiation.

### **TREATMENT**

RC is the preferred choice of treatment for UC. However, the patient strongly wished to preserve the bladder. We decided to administer preoperative neoadjuvant chemotherapy first, and evaluate whether RC should be performed according to the treatment effect. The standard treatment of preoperative neoadjuvant chemotherapy for MIBC is platinum-based cytotoxic chemotherapy, but the benefits in this complicated pathological type are unknown. In addition, IHC testing of tumor tissue showed that PD-L1 expression was positive, indicating that the patient might benefit from immunotherapy. Considering the high treatment efficacy of anti-PD-1 immunotherapy for MIBC and the patient's circumstances, he subsequently received chemotherapy combined with immunotherapy for bladder-sparing therapy. TURBT was performed to remove as much tumor tissue as possible, with the operative wound in the serosal layer of the bladder. The patient then received immunotherapy (tislelizumab) combined with chemotherapy (cisplatin/gemcitabine) every three weeks for four cycles. Cisplatin was administered at 70 mg/m<sup>2</sup> intravenously from the second day of the three-week cycle, gemcitabine was administered at 1000 mg/m<sup>2</sup> intravenously on day one and eight every three weeks and tislelizumab was administered 200 mg intravenously on day one of the three-week cycle.

Side effects during the treatment period included low-grade anemia, leukopenia and subclinical hypothyroidism. To evaluate the efficacy of immunotherapy combined with chemotherapy, the patient underwent pelvic MRI, cystoscopy and TURBT after two cycles of therapy. Pelvic MRI revealed no obvious nodules or masses on the posterior wall of the bladder and no enlarged lymph nodes around the iliac vessels (Figure 1B and 1F). Cystoscopy showed that the primary tumor site had been replaced by scar tissue (Figure 2B). The tissue sample collected during cystoscopy for pathological and IHC analysis showed no malignant characteristics. After four cycles of combination therapy, MRI demonstrated that there were still no nodules or masses in the bladder and the lymph nodes were the same as previously described (Figure 1C and 1G). Full-body positron emission tomography/computed tomography showed that the lesion described previously was obviously reduced without evidence of distant metastasis. Pathological examination results were also negative. All results indicated a marked response following the combination of chemotherapy and immunotherapy; thus, the next treatment strategy developed was immunotherapy, where tislelizumab was administered 200 mg intravenously on day one of the three-week cycle alone.

### **OUTCOME AND FOLLOW-UP**

The patient was advised to undergo MRI or cystoscopy every three months for the first year and every six months for the next two years to assess his condition.

The entire treatment period was two years, the patient was reexamined by MRI, and there was no recurrence of the tumor or enlarged lymph nodes (Figure 1D and 1H), which indicated that the patient was tumor-free with preserved bladder for almost two years. The overall treatment timeline is shown in Figure 5.

### **DISCUSSION**

Bladder cancer is one of the most common malignant neoplasms worldwide. More than 90% of these cancers are transitional cell carcinomas, which can also present mixed with other malignant components<sup>[5]</sup>. The mixed type of bladder histology includes squamous

differentiation (20-60% of bladder cancers), adenocarcinoma or glandular differentiation (10%), sarcomatoid (7%), micropapillary (3.7%), and lymphoepithelioma-like carcinoma<sup>5</sup>[2]. Thus, the identification of a histological variant type in UC is essential, which may be associated with different clinical outcomes and treatment strategies<sup>6, 7</sup>. Herein, we report a case of PD-L1 positive invasive UC with squamous and glandular differentiation. Considering the patient's strong desire for bladder preservation, bladder-sparing therapy with the combination of cisplatin/gemcitabine and tislelizumab was administered after TURBT. A marked response with no tumor or malignant features was observed following imaging and pathological examinations. Several studies have reported that the clinical phenotype of squamous and glandular differentiation was different to pure pathological types of UC. Adenocarcinoma is thought to have a poorer prognosis but has not been adequately studied to make definitive statements<sup>4</sup>[8]. It has been shown that pure adenocarcinoma is relatively resistant to chemotherapy and radiation, and there is no evidence that these treatments are beneficial in mixed tumors<sup>9</sup>. Besides, the significance of invasive UC with squamous and glandular differentiation at TURBT is still not confirmed, meaning no satisfactory and effective treatment has been found for this pathological type of UC<sup>10</sup>. However, research on a series of patients with variant histology found that UC with squamous or glandular or both types of differentiation often present with a higher pathologic stage, and significantly longer overall survival with cisplatin-based neoadjuvant chemotherapy ( $P = 0.024$ )<sup>11</sup>.

Although RC is the standard treatment for MIBC, some patients have a strong desire to preserve their native bladders due to poor quality of life after RC. Other treatment options for these patients are chemoradiotherapy or radiotherapy. In the present patient, the bladder tumor was relatively small with a maximum diameter of 42 mm. Radiotherapy will inevitably irradiate normal tissue, leading to adverse events such as gastrointestinal reactions, radioactive cystitis, skin damage, and some systemic side effects. In addition, RC is an alternative in the case of failed drug treatment, and the side effects of radiotherapy have great effects on the surgery. The effects of

radiotherapy on operating room tissue can also cause fibrosis, which leads to fixation of pelvic organs, making blunt dissection more difficult, and causes disruption of surgical landmarks and loss of tissue planes<sup>[12, 13]</sup>. Postoperative complications such as intestinal obstruction, poor wound healing, ureteral ileal anastomotic leakage and stenosis, lymphatic leakage, lower extremity venous embolism and cardiopulmonary, liver and kidney dysfunction can also increase. Some studies revealed that the rate of one or more complications in patients with RC and a history of pelvic radiotherapy is as high as 48% - 76%, which is significantly higher than that in patients without a history of pelvic radiotherapy (25.5% - 35.8%)<sup>[13,14]</sup>. In other studies, the perioperative mortality (0.8%) of RC in patients without a history of pelvic radiotherapy was lower than that (5.7%) in patients with a history of pelvic radiotherapy<sup>[14, 15]</sup>. Overall, radiotherapy was not considered the preferred treatment option for this patient.

Programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) blockade has been approved as a promising and effective treatment option for patients with advanced stage UC, and PD-L1 IHC expression has been shown to be involved in predicting immune checkpoint inhibitor therapy efficacy<sup>[1]</sup>. Five different anti-PD-1 (durvalumab, nivolumab and pembrolizumab) or anti-PD-L1 antibodies (atezolizumab and avelumab) have currently been approved for treatment of locally advanced or metastatic UC as second-line post-platinum-based chemotherapy, including atezolizumab<sup>[16]</sup> or pembrolizumab<sup>[17]</sup> and may be considered for cisplatin ineligible patients as first-line therapy if PD-L1 expression is positive. Moreover, in a single-arm phase 2 trial (NCT04004221/CTR20170071), tislelizumab (anti-PD-1 monoclonal antibody) as second-line therapy in PD-L1 positive (SP263) UC patients who progressed during/following platinum-containing therapy and had no prior PD-1/L1 inhibitor treatment achieved a confirmed objective response rate of 24% in 104 evaluable patients, including 10 complete and 15 partial responses. Median progression-free survival and overall survival were 2.1 and 9.8 mo, respectively<sup>[18]</sup>.

Different genetic mutations can influence immunotherapy efficacy. Six somatic mutations in our patient, including *ERBB2* p.S310F, *RB1* p.F404Lfs\*6, *ARID1A* p.S733\*,

*TERT c.-124C > T*, *TP53 p.R282W*, and *TP53 p.P152T*, were considered tumorigenic. *ERBB2* encodes an epidermal growth factor receptor, and its amplification can regulate cell growth by activating downstream signaling pathways<sup>[19]</sup>. A phase II trial showed that 18 patients with lung cancer carrying *ERBB2* mutations were treated with trastuzumab emtansine (T-DM1),<sup>11</sup> with an overall response rate of 44% and a median progression free survival of 5 mo<sup>[20]</sup>. Cells carrying the *S310F* mutation are sensitive to the *ERBB2* inhibitor and *ERBB2* monoclonal antibody<sup>[21]</sup>. However, there have been few studies on the other somatic mutations as biomarkers for the treatment of UC.

<sup>14</sup> TMB can be used as a marker for evaluating the effects of immunotherapy. Tumor cells with higher TMB are more easily recognized by the immune system and may have a stronger immune response to checkpoint inhibitors. In a clinical study, patients with non-small cell lung cancer<sup>13</sup> were divided into high and low TMB groups according to the median TMB, and the clinical benefit rates of the high and low TMB groups receiving pembrolizumab were 73% and 13% in the discovery cohorts, 83% and 22% in the validation cohorts<sup>[22]</sup>. Additionally, the TMB of melanoma patients who received ipilimumab and achieved long-term clinical benefits was significantly higher than that of melanoma patients who did not achieve long-term clinical benefits<sup>[23]</sup>.

In the present case, considering that PD-L1 IHC staining of tumor tissue was positive, the somatic mutation of *ERBB2 p.S310F*, and 51% TMB, a combination of chemotherapy and immunotherapy was finally chosen.

There are some limitations in this study. As the patient had a strong desire for bladder preservation, he did not undergo RC as the initial treatment which is recommended by the NCCN. Pathological specimens used for efficacy assessment were obtained by TURBT and thus there was possible undetected tumor tissue. Therefore, the pathology and follow-up results should be combined to comprehensively evaluate the treatment efficacy. In addition, the Food and Drug Administration has currently approved various PD-L1 assays for clinical use, usually corresponding to specific immune checkpoint inhibitors<sup>[24]</sup>.

<sup>3</sup>Analyses of the same sample using different assays may lead to discordant results, which might influence clinical treatment decisions. Furthermore, assuming that the cut-off value of the PD-L1 score applied <sup>3</sup>in clinical trials is intended to achieve statistically predefined results, it may not reflect a uniform tumor biological state<sup>[7]</sup>.

For accurate analysis, we reviewed a series of previous studies, based on PD-L1 assays (SP263) and cut-off values (TPS $\geq$ 25%) that were used in clinical trials of tislelizumab, and applied them to our case<sup>[18, 25]</sup>. Furthermore, to minimize manual error, automated quantification and interpretation of the PD-L1 IHC results were adopted in this case.

## **CONCLUSION**

We report a case of invasive UC with squamous and glandular differentiation and positive PD-L1 expression, for which there is currently no established therapy for such differentiation types. The tumor showed a marked response to the treatment with the combination of cisplatin/gemcitabine and tislelizumab, and the patient's bladder was successfully preserved. This case provides a new strategy for the treatment of patients with complex mixed histology MIBC. The combination of immunotherapy and chemotherapy for MIBC patients with positive PD-L1 expression may postpone the time to complete bladder resection and improve patient quality of life.

# 16%

SIMILARITY INDEX

### PRIMARY SOURCES

- |   |   |                |
|---|---|----------------|
| 1 | <a href="http://www.wjgnet.com">www.wjgnet.com</a><br>Internet  | 105 words — 4% |
| 2 | <a href="http://synapse.koreamed.org">synapse.koreamed.org</a><br>Internet  | 61 words — 2%  |
| 3 | <a href="http://www.nature.com">www.nature.com</a><br>Internet  | 45 words — 2%  |
| 4 | Siamak Daneshmand, Azadeh Nazemi. "Neoadjuvant Chemotherapy in Variant Histology Bladder Cancer: Current Evidence", European Urology Focus, 2020<br>Crossref  | 43 words — 1%  |
| 5 | <a href="http://link.springer.com">link.springer.com</a><br>Internet  | 34 words — 1%  |
| 6 | Dingwei Ye, Jiyang Liu, Aiping Zhou, Qing Zou et al. "Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma", Cancer Science, 2020<br>Crossref | 30 words — 1%  |
| 7 | <a href="http://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a><br>Internet  | 27 words — 1%  |
| 8 | Bohyun Kim, Cheol Lee, Young A. Kim, Kyung Chul Moon. "PD-L1 Expression in Muscle-Invasive Urinary  | 17 words — 1%  |

# Bladder Urothelial Carcinoma According to Basal/Squamous-Like Phenotype", Frontiers in Oncology, 2020

Crossref

9

[www.science.gov](http://www.science.gov)

Internet

16 words — 1%

10

[tessera.spandidos-publications.com](http://tessera.spandidos-publications.com)

Internet

15 words — 1%

11

Janakiraman Subramanian, Archana Katta, Ashiq Masood, Dashavantha Reddy Vudem, Rama Krishna Kancha. " Emergence of Mutation as a Biomarker and an Actionable Target in Solid Cancers ", The Oncologist, 2019

Crossref

14 words — < 1%

12

"Bladder cancer", Wiley, 2015

Crossref

13 words — < 1%

13

Fangchao Zhao, Yishuai Li, Zefang Dong, Dengfeng Zhang, Pengfei Guo, Zhirong Li, Shujun Li. "Identification of A Risk Signature Based on Lactic Acid Metabolism-Related LncRNAs in Patients With Esophageal Squamous Cell Carcinoma", Frontiers in Cell and Developmental Biology, 2022

Crossref

13 words — < 1%

14

Zhiquan Xu, Ling Xiang, Rong Wang, Yongfu Xiong, He Zhou, Haitao Gu, Jijian Wang, Linglong Peng. "Bioinformatic Analysis of Immune Significance of RYR2 Mutation in Breast Cancer", BioMed Research International, 2021

Crossref

12 words — < 1%

15

[www.thieme-connect.com](http://www.thieme-connect.com)

Internet

12 words — < 1%

---

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS