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Case Report

Use of Pembrolizumab in End-Stage Renal Disease: A Case Report with Complete Response

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Keywords
Urothelial carcinoma · Immunotherapy · Renal disease · Hemodialysis

Abstract
Second-line treatment in urothelial carcinoma is not well defined. Immunotherapy has shown good outcomes in this setting, but it has not been tested in patients with end-stage renal disease (ESRD). We present a clinical case describing the use of pembrolizumab in a patient under hemodialysis (HD) that achieved a complete response. A 72-year-old man was diagnosed with urothelial carcinoma in 2001. Following transurethral resection of the bladder tumor, bacillus Calmette-Guérin, and mitomycin treatment, he underwent surgery in 2018. The patient required HD since surgery. A few months after surgery, there was disease progression with lung metastasis. A first-line treatment with carboplatin and gemcitabine was started, but after 5 cycles, disease progression was confirmed. It was decided to initiate second-line treatment with pembrolizumab. After 13 months of immunotherapy, a CT scan showed a complete response with total involution of lung metastasis. Immune checkpoint inhibitors are an option to second-line treatment in urothelial carcinoma. Further studies are needed to clarify the efficacy and tolerance of this therapy in ESRD patients.

Introduction

Bladder cancer is the most common malignancy involving the urinary system, and urothelial carcinoma is the predominant histological type in Europe, accounting for 90% of cases. Systemic treatment with platinum-based chemotherapy is the standard choice for

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patients with metastatic disease. The median survival of these patients is approximately 15 months [1]. After a first-line treatment with chemotherapy, there is no consensus regarding second-line options. Immune checkpoint inhibitors (ICIs) have been associated with better outcomes in the treatment of solid tumors, including bladder cancer. Pembrolizumab has been tested in phase 1b KEYNOTE-012 and phase 2 KEYNOTE-052 trials and showed anti-tumor activity in urothelial carcinoma [2, 3]. KEYNOTE-045, a phase 3 trial, confirmed longer overall survival (OS) with pembrolizumab in patients with platinum-refractory advanced urothelial cancer compared with other options of treatment, such as chemotherapy [4]. End-stage renal disease (ESRD) is a challenge in cancer patients because it limits treatment choice due to the risk of toxicity. Patients with ESRD are often excluded from clinical trials. We present a case describing the use of pembrolizumab in a patient with ESRD on hemodialysis (HD).

Case Presentation

A 72-year-old man, former smoker (pack years 12), without comorbidities, presented in 2001 with gross hematuria. A diagnosis of early-stage bladder cancer was made (pTa) in a urology consultation. During the following years, he was submitted to several transurethral resections of the bladder tumor, bacillus Calmette-Guérin, and mitomycin treatments. In May 2018, he underwent bilateral nephrectomy, cystoprostatectomy, and ureterectomy. The histological diagnosis was consistent with high-grade papillary urothelial carcinoma, multifocal, pT2(m). The patient required HD since surgery. A CT scan in December 2018 identified multiple bilateral pulmonary metastases with dimensions less than 2 cm. A pulmonary biopsy was compatible with urothelial carcinoma metastasis. PDL-1 quantification was not possible to determine due to insufficient sample. Treatment with chemotherapy was started in May 2019 with carboplatin (AUC 4) and gemcitabine (800 mg/m^2). After 5 cycles, a CT scan confirmed disease progression with increased size of previously existing pulmonary lesions and the appearance of new lesions. In October 2019, it was decided to start second-line treatment with immunotherapy, specifically pembrolizumab 200 mg every 3 weeks. After 3 months, in January 2020, an imagiological reassessment showed reduction of lung metastasis, which was considered to be a partial response. Regarding toxicities, the patient had grade 1 skin rash and pruritus that resolved after antihistamine treatment. After 13 months of pembrolizumab, a CT scan confirmed a complete response with complete involution of lung metastasis.

Discussion

The standard treatment of metastatic urothelial carcinoma is chemotherapy with a platinum scheme. However, the efficacy of systemic chemotherapy is often limited, with an overall response rate of 50–70%, a median progression-free survival of 7–9 months, and a median OS of 12–15 months [5]. Results of second-line treatments have shown poor outcomes, and the only chemotherapy approved as second-line treatment in Europe is vinflunine, with only modest responses [6]. Another option in second-line treatment is a rechallenge with platinum chemotherapy in patients with a later progression after first-line treatment [1]. Moreover, treatment options in second-line treatment are conditioned by renal function, commonly impaired as a consequence of toxicities of first-line treatment as well as by the underlying disease. ICIs, such as pembrolizumab, have been tested in this setting. In the KEYNOTE-045 trial, pembrolizumab has shown a better response and survival compared

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with chemotherapy. OS was longer in the pembrolizumab arm compared with the chemotherapy arm (10.3 months vs. 7.4 months), and the benefit was independent of PDL-1 expression. Objective response was also better with pembrolizumab (21.1% vs. 11.4%), and there were fewer treatment related adverse events compared with chemotherapy [4]. Other ICIs are currently approved for metastatic urothelial carcinoma treatment, showing higher response rates and survival benefits compared with chemotherapy [7, 8].

Renal function conditions treatment selection, being it chemotherapy or ICIs. Despite ESRD not being an absolute contraindication to the administration of cancer drugs, these patients are in a greater risk of developing toxicity due to increased drug exposure. Another challenge is the inefficient drug exposure because of early extensive elimination through dialysis. In fact, the CANcer and DialYsis (CANDY) study assessed the management of cancer drugs in dialysis patients and showed that 72% of these patients received at least one drug that required dose adjustment [9]. This study highlighted the importance of dose adjustment according to the available recommendations. However, ICIs have not been studied.

Pembrolizumab is approved for patients with mild to moderate renal impairment, but it has not been studied in patients with severe renal impairment. Currently, there are few published data on the use of ICIs in HD-dependent patients. Published case series report a variety of malignancies treated with different ICIs in ESRD like melanoma, renal cell carcinoma, or non-small-cell lung cancer [10–13]. The immune-related adverse events occurred in a small number of patients and were not more frequent compared with patients without renal dysfunction. A retrospective study that included 8 patients with different types of cancer treated with ICIs showed that immunotherapy seemed to be safe in ESRD patients without the need for dose adjustments [11]. Another retrospective study in 8 patients with metastatic renal carcinoma treated with nivolumab also described that the tolerability and safety of ICIs was similar to non-ESRD patients, with no unexpected adverse events registered [13].

In our clinical case, pembrolizumab demonstrated an excellent outcome with complete response. We chose a scheme without dose adjustment, keeping the standard recommended dose of 200 mg every 3 weeks. The treatment was well tolerated and only with mild immune-related adverse events despite the patient being under HD.

Conclusion

Immunotherapy has changed the treatment of metastatic urothelial carcinoma. Our clinical case reports a complete response of lung metastases with pembrolizumab in a patient under HD. Further studies are needed to analyze the efficacy and tolerability of ICIs in patients with ESRD and, specifically, under HD.

Statement of Ethics

The patient gave written informed consent to publish the case. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Marina Vitorino drafted the manuscript and contributed on the interpretation of data. Catarina Santos revised the manuscript and contributed on the interpretation of data. All the authors have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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