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Advanced cervix cancer patient with chemotherapy-induced grade IV myelosuppression achieved complete remission with cadonilimab: A case report

Zhu R *et al.* Treatment with bispecific antibodies

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Abstract

BACKGROUND

The prognosis for patients with advanced metastatic cervix cancer (MCC) is poor, and this disease continues to pose a considerable therapeutic challenge. Despite the administration of first-line regimens consisting of cisplatin, paclitaxel, and bevacizumab, survival rates for patients with metastasis remain poor. The emergence of bispecific antibodies (BsAbs) offers a novel treatment option for patients diagnosed with MCC.

CASE SUMMARY

In this report, we present a patient with MCC who was treated with cadonilimab monotherapy at a dose of 6 mg/kg every two weeks after chemotherapy was proven to be intolerable. The patient exhibited a sustained complete response for a duration of 6 months, demonstrating an optimistic outlook.

CONCLUSION

This case illustrates the considerable efficacy of cadonilimab for treating advanced MCC. Therefore, BsAb therapy is a promising strategy for effectively treating patients

with advanced MCC and should be considered as an option when patients are intolerant to standard chemotherapy.

Key Words: Cadonilimab; Complete response; Bispecific antibodies; Recurrent or metastatic cervical cancer; Programmed death protein 1; Cytotoxic T-lymphocyte-associated antigen-4; Case report

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Core Tip: Advanced metastatic cervical cancer (MCC) has a poor prognosis and a low survival rate. The emergence of bispecific antibodies offers a novel treatment option for patients with MCC. Cadonilimab is a tetravalent bispecific antibody designed to simultaneously block the programmed death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathways while substantially reducing toxicities compared to combination therapy with PD-1 and CTLA-4 antibodies. We report the case of a patient with advanced MCC who achieved a complete response with cadonilimab monotherapy despite chemotherapy-induced grade IV myelosuppression.

INTRODUCTION

Among all cancers, cervix cancer (CC) is the fourth most common cancer among women worldwide, following breast, colorectal, and lung cancer. The average age at diagnosis of CC globally is 53 years, while the average age at death is 59 years^[1]. Additionally, CC ranks as the fourth leading cause of cancer-related deaths in women, following breast, lung, and colorectal cancers. Surgery remains the primary treatment option for early-stage CC, while concurrent radiotherapy is commonly employed for intermediate-stage and advanced-stage CC. Even when patients are treated with the first-line regimen of

cisplatin and paclitaxel combined with bevacizumab, the median overall survival (mOS) for patients with recurrent or metastatic cervical cancer (R/MCC) is only 17.0 months^[2]. R/MCC is widely considered an incurable condition. The advent of immunotherapy in recent years has provided a promising avenue for treating R/MCC.

In the past two decades, tumor immunotherapy has emerged as a prominent modality in combination with surgery, radiation therapy, or chemotherapy for cancer treatment. The emergence of immune checkpoint inhibitors (ICIs), such as programmed death protein 1 (PD-1)/programmed death protein 1 ligand (PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), has revolutionized cancer immunotherapy on a global scale^[3]. However, the advent of PD-1/CTLA-4 bispecific antibodies (BsAbs) offers a novel and highly specific treatment option that demonstrates enhanced efficacy for patients with R/MCC who have experienced failure with previous platinum-containing chemotherapy^[4]. In this context, we present a comprehensive account of the process involved in achieving complete response (CR) following treatment with PD-1/CTLA-4 BsAb in a patient diagnosed with advanced metastatic cervix cancer (MCC) and grade IV myelosuppression after chemotherapy.

CASE PRESENTATION

Chief complaints

A 59-year-old woman was admitted to the oncology department of our hospital (the First Affiliated Hospital of Soochow University) due to vaginal metastasis of CC, seeking further treatment.

History of present illness

Chemotherapy could not be continued due to grade IV myelosuppression induced by chemotherapy.

History of past illness

The patient presented to the Second Affiliated Hospital of Soochow University in June 2021 with a 2-month history of abnormal vaginal bleeding. Specialized examination revealed the presence of a cauliflower-like mass in the cervix. After laparoscopic extensive total uterus removal, bilateral adnexectomy, bilateral pelvic infundibular ligament high ligation, and pelvic lymphadenectomy, postoperative pathology confirmed the diagnosis of extensive squamous cell carcinoma involving the entire uterus and both adnexa. Adjuvant chemoradiotherapy was administered following the surgical intervention.

In November 2021, a mass was identified in the vaginal wall and confirmed to be squamous cell carcinoma through biopsy and related pathological and immunohistochemical findings. A total of 28 radiotherapy sessions were performed at the Second Affiliated Hospital of Soochow University, starting in December 2021. Additionally, the patient received three cycles of intravenous chemotherapy with paclitaxel combined with carboplatin from January to April 2022. Chemotherapy was discontinued due to the occurrence of grade four bone marrow suppression.

Personal and family history

The patient had a documented history of hypothyroidism and consistently adhered to the prescribed medication. She had a family history of genetic disease, history of other chronic diseases, history of cancer, etc.

Physical examination

A detailed general examination of the patient was performed and no obvious positive signs were found.

Laboratory examinations

On July 8, 2022, the female tumor marker levels were as follows: CEA, 146 ng/mL; CA125, 94 IU/mL; and CA199, 83.1 IU/mL (Table 1). The following three indicators of thyroid function were measured: T4, 54.9 nmol/L; TSH, 31.5 μ IU/mL; and TPO-Ab, 941

IU/mL (Table 1). No abnormalities were found in routine blood, biochemical, or cardiac activity.

Imaging examinations

Computed tomography (CT) revealed notable metastases in both the lungs and liver (Figures 1A and 2A).

FINAL DIAGNOSIS

The patient was diagnosed with cervical squamous cell cancer accompanied by vaginal metastasis, and the disease stage was determined to be T1N0M1 (IVB).

TREATMENT

After excluding contraindications, cadonilimab 6 mg/kg q2w was administered for immunotherapy. Figure 3 illustrates the diagnosis and treatment of the patient.

OUTCOME AND FOLLOW-UP

On August 27, 2023, we reexamined the patient's chest and abdomen CT and observed considerable improvement in multiple lung and liver metastases (Figures 1B and 2B). The levels of CEA (22,500 ng/mL), CA125 (17,300 IU/mL), and CA199 (18.40 IU/mL) were lower than their previous values (Table 1). Thyroid function was assessed on August 27, 2022, with a T3 level of 1.01 nmol/L, a T4 level of 62.90 nmol/L, a TSH level of 90.100 μ IU/mL, and a TPO-Ab concentration exceeding 1000 IU/mL (Table 1); the Euthyrox dosage was increased from 25 μ g qd to 75 μ g qd orally due to considerations related to immune medications. No other immune-related side effects were observed during the comprehensive evaluation of partial response (PR). Assessments of the patient's condition were scheduled for October 28, 2022; January 18, 2023; April 27, 2023; and July 24, 2023 (Table 1, Figure 1C-F and Figure 2C-F). We were pleased to find that on April 27, 2023, the patient achieved CR according to the Revised Response Tumors (RECIST) guidelines (version 1.1) and maintained CR until July 24, 2023 (the

time of most recent assessment).¹ We will continue to follow up with the patient and strictly review the changes in her conditions.

DISCUSSION

Here, we report the efficacy, feasibility, and tolerability of cadonilimab monotherapy in patients diagnosed with MCC who previously underwent platinum-based chemotherapy but experienced treatment failure. The patient did not experience any adverse effects during treatment with cadonilimab; however, the Euthyrox dosage was increased from 25 µg qd to 75 µg qd due to considerations related to immune medications.

The first-line treatment option for R/MCC consists of carboplatin, paclitaxel, and bevacizumab. However, this disease is often curable and is typically associated with a limited survival rate when treated using conventional methods^[5]. The landscape of cancer treatment has substantially transformed in recent decades with immunotherapies, particularly ICIs for which PD-1, PD-L1, and CTLA-4 are targeted. These treatments are increasingly used for CC.

The combination of CTLA-4 and PD-1 inhibitors has received approval for three indications, namely,³ metastatic melanoma (MM), advanced renal cell carcinoma, and colorectal cancer with MMR and MSI-H aberrations^[6]. Extensive investigations have been conducted on the combination of CTLA-4 and PD-1 inhibitors in patients with MM, demonstrating the efficacy of this combination across multiple clinical trials. The³ combination of nivolumab and ipilimumab in previously untreated patients with advanced melanoma, as demonstrated in a phase 1 trial (NCT01927419) conducted by Postow *et al*^[7], resulted in a significantly improved objective response rate and progression-free survival compared to those from treatment with ipilimumab alone. Notably, 22% of the participants achieved CR. The subsequent findings from a phase 2 trial (NCT01927419) conducted by Hodi *et al*^[8] revealed a significant improvement in the two-year overall survival rate among patients who received nivolumab and ipilimumab compared with those who received only ipilimumab as treatment (63.8% *vs*

53.6%). The Landmark Check Mate 067 clinical trial (NCT01844505) assessed the efficacy of combination therapy with nivolumab plus ipilimumab compared to that of monotherapy with either nivolumab or ipilimumab in a cohort of 945 patients diagnosed with stage III or IV melanoma. The mOS was observed to be more than 60 months in the cohort receiving nivolumab plus ipilimumab, whereas it was 36.9 months and 19.9 months in the cohorts receiving nivolumab alone and ipilimumab alone, respectively. The 5-year overall survival rates were 52%, 44%, and 26%, respectively. Although combination therapy has previously demonstrated potential improvements in OS, these improvements are accompanied by an increasing incidence of adverse events^[9,10].

Cadonilimab is a tetravalent BsAb designed to simultaneously block the PD-1 and CTLA-4 pathways while significantly reducing toxicity compared to combination therapy with PD-1 and CTLA-4 antibodies^[11]. Moreover, a study conducted by Wei *et al*^[12] revealed that the combined administration of CTLA-4 and PD-1 inhibitors demonstrated superior clinical efficacy; however, it was accompanied by more pronounced adverse reactions than was cadonilimab. The emergence of cadonilimab, a novel pharmaceutical compound, occurred during this period^[4]. The approval of cadonilimab for R/MCC by the China National Medical Products Administration in June 2022 was based on promising results obtained from clinical trials^[13]. The patient in this case met the criteria and responded well to monotherapy, ultimately achieving CR during the comprehensive evaluation. However, this is not an isolated case. The 2022 CACA guide to China-cervical cancer highlights an important significant case presented at the "Southern Tour" academic conference, where Professor Li Xiaofan from Peking University Cancer Hospital shared a compelling case of advanced CC that garnered considerable attention. In this case, after initial-line chemotherapy failed, the patient underwent radiotherapy and subsequently experienced progression. Due to adverse reactions, the patient subjectively resisted further chemotherapy and subsequently achieved remission after only 2 cycles of treatment with cadonilimab immunotherapy,

followed by PR after 4 cycles, for a total of 8 cycles of therapy, with the effect approaching CR.

Four completed single-agent studies of cadonilimab (AK104-101, AK104-201, AK104-202 and AK104-204) were conducted to investigate the efficacy of this drug in various tumor types, including cervical cancer, nonsmall cell lung cancer, nasopharyngeal cancer, hepatocellular carcinoma, esophageal cancer, mesothelioma, melanoma, colorectal cancer, stomach cancer, endometrial cancer, ovarian cancer, breast cancer, renal cell carcinoma, small cell lung cancer, neuroendocrine tumors, prostate adenocarcinoma, head and neck squamous cell carcinoma, pancreatic ductal adenocarcinoma, and cholangiocarcinoma. In a case report by Jieqiong Peng *et al.*, a patient diagnosed with stage IV HER-2-positive gastric adenocarcinoma who presented with advanced liver and lung metastases was documented. The patient was enrolled in a clinical trial (NCT03852251) and achieved CR following treatment with cadonilimab combined with chemotherapy. However, immune-associated pulmonary toxicity and hepatitis related to treatment were observed^[14].

Cadonilimab is one of the many BsAbs. To date, a total of seven BsAbs have received marketing approval worldwide, namely, catumaxomab (which was withdrawn from the market in 2017), blinatumomab, emicizumab, amivantamab, faricimab, cadonilimab, and mosunetuzumab. Additionally, more than 200 BsAbs are currently undergoing clinical and preclinical research stages^[15].

The patient in this case had to receive single-agent cadonilimab due to grade 4 bone marrow suppression resulting from chemotherapy. We next investigated the potential synergistic effects of combining cadonilimab with radiotherapy and chemotherapy in future clinical treatments. Moreover, we must be attentive to the potential occurrence of complications resulting from the combination of radiotherapy, chemotherapy, and immunotherapy.

CONCLUSION

This case demonstrated the marked effectiveness of single-agent cadonilimab treatment in patients with advanced MCC in which chemotherapy was not well tolerated. The therapy was well tolerated; however, vigilant monitoring for immune-related adverse events is recommended for patients with a prior medical history. BsAbs offer a promising therapeutic approach for patients with advanced MCC and should be considered an option after standard chemotherapy fails.

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