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Good Response to Cadonilimab (PD-1/CTLA-4 Bi-specific Antibody) Combined with Chemotherapy as First-line Treatment in Superaged Patient with HER2-Negative Advanced Gastric Cancer: A Case Report

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1. Abstract

Gastric cancer remains a considerable global health burden, with limited treatment options available for advanced cases, especially for the superaged patients (> 80 years as defined by the World Health Organization). Bi-specific antibodies (BsAbs) offer a promising therapeutic approach by targeting two distinct antigens simultaneously, thereby enhancing specificity and potency. Cadonilimab (AK104), a first-in-class BsAb targeting PD-1/CTLA-4, exhibits similar biological activity but lower toxicity compared to the combination of CTLA-4 and PD-1 antibodies. Herein, we present a case report of an 85-year-old patient with HER2-negative advanced gastric cancer who received first-line treatment with cadonilimab combined with chemotherapy regimen, but cadonilimab was discontinued and only single-agent chemotherapy was used due to the observation of immune-related pneumonitis during treatment. Despite these changes, the patient still exhibited a stable disease (SD) condition for a year until now. This case report highlights the potential of cadonilimab in the first-line treatment of superaged patients with advanced gastric cancer, while future studies are warranted to further evaluate and balance the efficacy and safety of this novel immunotherapy approach.

2. Introduction

Gastric cancer, with gastric adenocarcinoma as the most common histological type, is the fifth most common cancer and the third most leading cause of cancer death worldwide [1-2]. However, elderly patients account for a large proportion of gastric cancer [3]. Despite advances in treatment strategies, the prognosis for elderly patients with HER2-negative advanced gastric adenocarcinoma remains poor due to gradual loss of immunonutritional and functional status, with higher mortality rates and more limited treatment options [4]. With the publication of the data of CheckMate-649 clinical trial, immunotherapy (immune checkpoint inhibitors, ICIs) combined with chemotherapy have gradually become a new standard first-line treatment for patients with HER2-negative advanced gastric adenocarcinoma [5]. Cadonilimab, the world's first BsAb that targets PD-1 and CTLA-4 immune checkpoint simultaneously to activate the immune system to attack and eradicate tumor cells, can fully exert the synergistic anti-tumor effect of ICIs against PD-1 and CTLA-4, while the side effects are significantly reduced compared with the combined treatment of PD-1 and CTLA-4 monoclonal antibodies[6-8], which was further confirmed by the data of the COMPASSION-15 Phase III clinical trial of first-line immunotherapy with cadonilimab plus chemotherapy for advanced gastric cancer, presented at the recent AACR Annual Meeting 2024[9]. Here, we report a case of cadonilimab combined with chemotherapy as the first-line treatment for a superaged patient with HER2-negative advanced gastric adenocarcinoma.

3. Case Presentation

An 85-year-old male has no clear inducement to present dysphagia with no other discomfort in October 2022. Subsequently, symptoms gradually worsen. On 1 February 2023, gastroscopy performed in our hospital revealed: esophageal congestion, edema and erosion, cardia stenosis and ulcer, implicating the gastric fundus (Figure 1a). Biopsy pathology: poorly differentiated gastric cardia adenocarcinoma (Figure 1b). Computed tomography (CT) of the cervicothoracic abdomen and pelvis: gastric space-occupying lesion, enlarged lymph nodes in the hepatogastric ligament and retroperitoneum, and low-density shadow in the left lobe of liver (Figure 1c). Immunohistochemistry (IHC) analysis: PD-1 (-), C-erbB-2 (1+), MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), PD-L1 (22C3) CPS=5. In situ hybridization (ISH): EBER (-). PET/CT showed gastric hypermetabolic space-occupying lesion, consistent with the sign of malignant lesion; slightly hypermetabolic enlarged lymph nodes in bilateral hilus pulmonis, mediastinum, and retroperitoneum, multiple non-metabolic small nodules in both lungs (Figure 1d). After comprehensive consideration (advanced age; surgical risks and complications), the patient and his family refused surgical treatment and radiation therapy, and requested immunotherapy combined with systemic chemotherapy. After excluding contraindications for chemotherapy, the treatment of oxaliplatin 110 mg d1 + fluorouracil 0.5 g iv d1, 3.0 g civ 46h + cadonilimab 360 mg d4, q2w was commenced on 24 February 2023. After one cycle of treatment, the patient developed fever, accompanied by rhinorrhea and cough with yellow sputum. A routine blood test showed a decrease in white blood cells and chest CT showed bilateral pulmonary inflammation (Figure 2a). The patient was considered to have bacterial and virus coinfection. The symptoms of cough and expectoration were alleviated after symptomatic treatment, and there was no recurrence of fever. Subsequently, five cycles of oxaliplatin 110 mg d1 + fluorouracil 0.5 g iv d1, 3.0 g civ 46h + cadonilimab 360 mg d4, q2w was initiated on 31 March 2023. A stable disease (SD) condition was assessed by CT after three cycles of treatment (Figure 3a). The follow-up gastroscopy and CT examination showed the improvement in gastric cardia and surrounding lymph nodes. However, there was a slight aggravation in interstitial fibrosis of both lungs and a slight enlargment in mediastinal lymph nodes (Figure 3b-c). After a full-scale discussion, it was clinically considered that the mediastinal lymph nodes were more likely to be benign lesions, and good local control of the stomach was achieved. Considering the patient's advanced age and significant decline in physical condition, we adjusted the regimen to cadonilimab 345 mg d1 + tegafur 40 mg bid d1-14 of maintenance therapy for four cycles on 30 June 2023 and the patient felt that the sense of swallowing obstruction was alleviated than before. The chest CT examination on September 8, 2023 revealed interstitial lesions and microscopic nodules in both lungs, and calcification in the upper lobe of the right lung (Figure 2b). After communicating with the patient's family, we discontinued cadonilimab and used tegafur monotherapy of 40mg bid d1-14 instead. As of February 27, 2024, the patient remained in a stable condition (Figure 3a).

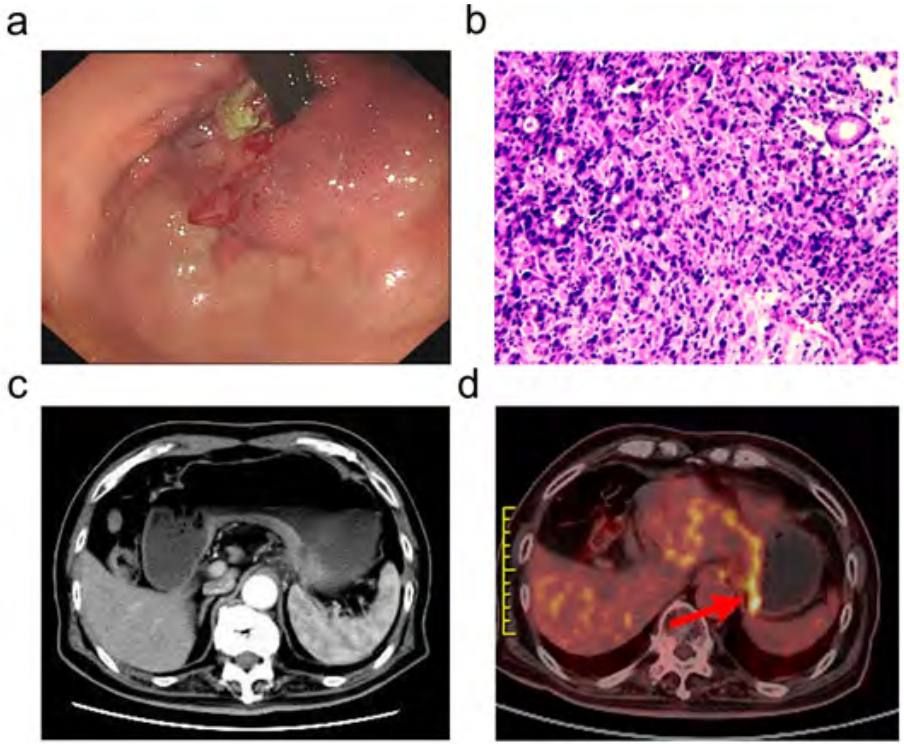

Figure 1: The images taken at baseline before treatment. (a) The image of gastroscopy. (b) The image of hemotoxylin and eosin (H&E): poorly differentiated adenocarcinoma (cardia). (c) The image of computed tomography (CT) of the cervicothoracic abdomen. (d) The image of PET/CT: gastric space-occupying lesion of hypermetabolic malignancy.

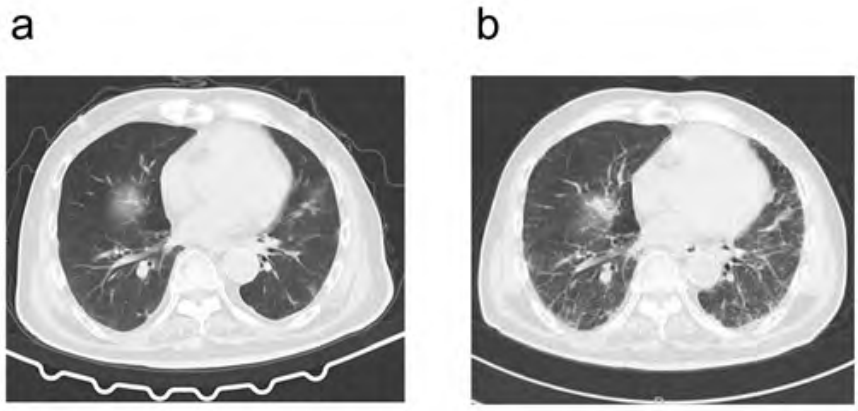

Figure 2: Side effects that occurred during the treatment of immunotherapy. (a) Chest CT imaging of pneumonia in the bilateral lungs during immunotherapy combined with double-agents chemotherapy. (b) Chest CT showed interstitial lesions of both lungs during immunotherapy combined with single-agent chemotherapy.

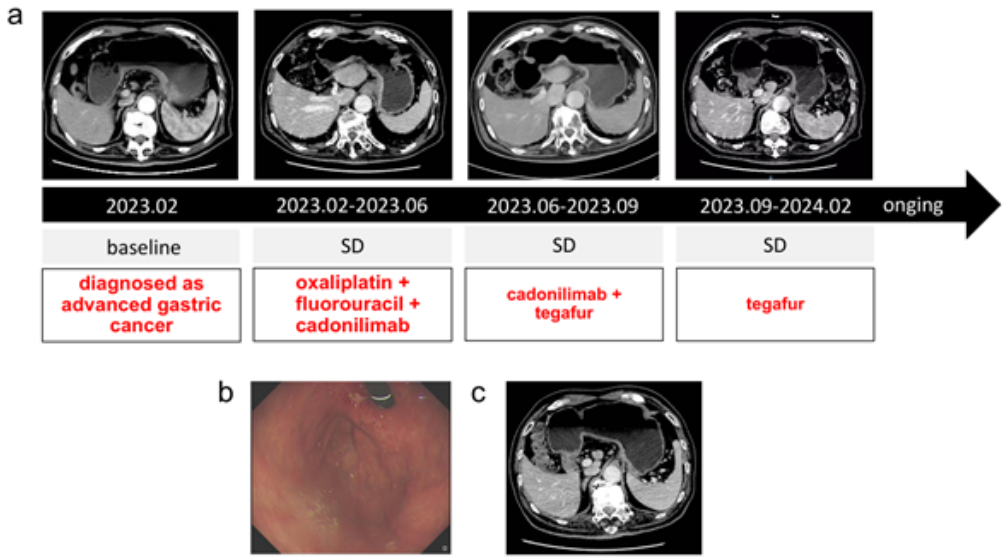

Figure 3: Effectiveness of immunotherapy combined with chemotherapy. (a) Sequence of CT scan changes across the antitumor treatment timeline: oxaliplatin + fluorouracil + cadonilimab; cadonilimab + tegafur; tegafur. (b-c) The gastroscopy and CT showed the improvement in gastric cardia and surrounding lymph nodes after the treatment of immunotherapy combined with chemotherapy.

4. Discussion

This paper reports the efficacy and safety of a superaged patient with HER2-negative advanced gastric cancer received the first-line treatment of immunotherapy combined with chemotherapy. In previous clinical studies, the age limit for immunotherapy was typically set at 75 years old and the safety of the use of ICIs needs to be evaluated more carefully for such superaged patients due to the relative weaker physiological immune function and lower drug tolerance. However, the family strongly requested the use of cadonilimab (a unique anti-PD-1/CTLA-4 BsAb) despite the age restriction because the patient desperately needed a better treatment option. After six cycles of treatment with cadonilimab combined with double-chemotherapy, the tumor volume of the patient decreased significantly and the symptoms of the disease stabilized, reaching the SD state. However, due to the occurrence of immune-related pneumonitis, a known side effect of immunotherapy, the plan was adjusted to cadonilimab plus tegafur single-chemotherapy after symptomatic treatment. After four cycles of treatment, the patient's condition was poor, and hence cadonilimab was suspended and only tegafur monotherapy was continued after communicating with his family. The treatment of cadonilimab was not restarted subsequently in view of the poor basic condition of the patient. As of 27 February 2024, the disease has been remaining the SD state and the PFS of the patient is nearly 12 months. It is very satisfactory for an 85-year-old patient with such a treatment effect. This case brings us several insights. Firstly, cadonilimab combined with chemotherapy appears to be an effective treatment for superaged patients with HER2-negative advanced gastric can-

cer, as supported by the positive results in COMPASSION-15 study, showing that the primary and secondary endpoints of the clinical trial were achieved in all ITT populations and cadonilimab combination regimen can benefit the patients regardless of PD-L1 expression status (PD-L1 CPS≥5 or PD-L1 CPS＜5)[9]. Furthermore, we also found the development of immune-related pneumonitis in the previous studies of cadonilimab, the same adverse reaction that also can be seen in other immunotherapy drugs [10-12]. However, some restarted cadonilimab after hormone treatment. In contrast, we discontinued instead of restarting it due to the poor physical condition of the patient, and the disease currently remains in a stable state, but whether the achievement of this state is due to the lingering effect of cadonilimab remains a question worthy of further discussion. Additionally, whether the patient can achieve a better state if we restarted it is also a question deserving further investigation. Moreover, we are also concerned whether recurrent immune-related pneumonitis or more serious adverse reactions will occur if we restart it, which is the main reason why the patient's family disagreed to restart it. Overall, we need to consider the risk-benefit ratio when using cadonilimab, particularly in superaged patients.

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7. Conflict of Interest

The authors declare no conflict of interest in preparing this article.

8. Authors' Contribution

Conception and design: Qian Wang. Data acquisition and analysis: Jia Lun, Guikai Ma. Manuscript draft: Jia Lun, Qian Wang. Manuscript revision: Xuan Wang. All authors reviewed and approved the final manuscript.

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