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Case Report

Camrelizumab for Preemptive Treatment of Molecular Recurrence after Allogeneic Hematopoietic Stem Cell Transplantation in Core-Binding Factor Acute Myeloid Leukemia: Two Case Reports

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ABSTRACT: This paper reports two patients with core-binding factor AML (CBF-AML) who experienced molecular recurrence following allogeneic hematopoietic stem cell transplantation (allo-HSCT). They were given preemptive treatment with camrelizumab, an inhibitor of programmed cell death protein 1 (PD-1). In case 1, a 45-year-old male AML patient with persistent CBFβ-MYH11 fusion transcripts received allo-HSCT after complete remission (CR). After transplantation, CBFβ-MYH11 fusion transcript remained persistently positive even after treatment with the hypomethylating agent decitabine. Camrelizumab was administered eight months post-transplantation. After 3 cycles administered at two-week intervals, the CBFβ-MYH11 transcripts became negative. Only mild liver insufficiency and telangiectasia were observed. In case 2, a 20-year-old male AML patient with the AML1-ETO fusion gene experienced molecular recurrence post allo-HSCT, even after treatment with decitabine. Camrelizumab was then administered 1 year after transplantation. After 2 cycles, AML1-ETO transcripts gradually became negative. However, severe immune-related liver injury occurred. Liver function eventually recovered with treatment. In conclusion, PD-1 inhibitors may be an effective strategy for CBF-AML patients with late stage molecular recurrence after allo-HSCT and should be explored further.

Keywords: Acute myeloid leukemia; Allogeneic hematopoietic stem cell transplantation; Camrelizumab; Molecular recurrence; Preemptive treatment

1. Introduction

Acute myeloid leukemia (AML) is among the most aggressive hematological malignancies affecting adults [1]. Although the complete remission (CR) rate and overall survival (OS) of AML increased in recent years, more than 50% of AML patients will eventually relapse. Hematopoietic stem cell transplantation (HSCT) is a curative therapy for AML patients, as it clears out residual leukemia cells and enhances the graft versus leukemia (GVL) effect. However, nearly 20% of patients will still relapse after transplantation. To prevent this, regular monitoring and preemptive treatment for measurable residual disease (MRD) after transplantation are widely used [2]. In adult AML, MRD information can predict relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [3]. A higher cumulative recurrence rate was confirmed in patients with persistent positive MRD after allo-HSCT compared to patients with negative MRD [4]. In preemptive treatment, therapies such as conventional chemoradiotherapy, targeted therapy, donor lymphocyte infusion (DLI) and chimeric antigen receptor T cells (CAR-T) therapy can be used based on guideline recommendations and the practice experience of different hospitals. However, these treatments only apply to a few patients due to the lack of donors, severe graft versus host disease (GVHD), drug resistance, lack of optimal targets, and other reasons.

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Immune checkpoint inhibitors, such as programmed cell death 1 (PD-1), inhibitors are widely used in solid tumors and hematological malignancies based on the expressions of PD-1 ligands on tumor cells and microenvironments, which contribute to tumor immune escape [5]. Camrelizumab, a PD-1 inhibitor, was approved in China in 2019 for the treatment of relapsed or refractory Hodgkin's lymphoma [6,7]. According to the literature, the recurrence rate was significantly reduced, and the progression-free survival was significantly improved [8]. The adverse effects of camrelizumab include immune-related adverse events (irAEs) in the early stages, similar to other PD-1 inhibitors. It is reported that PD-1 can be induced on the surface of certain T cells, contributing to T cell exhaustion and leukemia relapse. Theoretically, PD-1 inhibitors can be used after allo-HSCT to prevent leukemia recurrence. However, this approach is challenging due to the risk of severe GVHD after PD-1 inhibition.

In this study, we reported that two CBF-AML patients with molecular recurrence after allo-HSCT underwent preemptive treatment with camrelizumab. MRD was cleared in both patients, but the irAE needs to be carefully identified and managed.

The study was approved by the Ethics Committee of the General Hospital of Western Theater Command, People's Liberation Army. Patients provided written informed consent to participate in this study. All methods were carried out in accordance with the Declaration of Helsinki.

2. Case Presentation

2.1. Case 1

A 45-year-old man was diagnosed with AML with the CBFβ-MYH11 fusion gene in January 2020. CBFβ-MYH11 transcripts were monitored throughout the course of the disease using reverse-transcription polymerase chain reaction (RT-PCR) (Figure 1). The patient achieved complete remission (CR) after several cycles of chemotherapy but with persistent MRD. He was then treated with allo-HSCT in September 2020. After allo-HSCT, MRD detected by flow cytometry was negative, but the CBFβ-MYH11 transcript was positive (0.086%, fusion transcript copies/ABL copies). Several cycles of a 3-day decitabine regimen (10 mg/day) were used to prevent leukemia relapse. However, the patient did not obtain molecular remission. He was then prescribed camrelizumab 200 mg for 3 cycles at two-week intervals. On day 270 post-transplantation, the CBFβ-MYH11 transcript eventually turned negative (Figure 1). Regarding safety, camrelizumab induced reversible grade III liver damage, which might be considered an irAE (Figure 2). The MRD and liver function remained normal during regular follow-up.

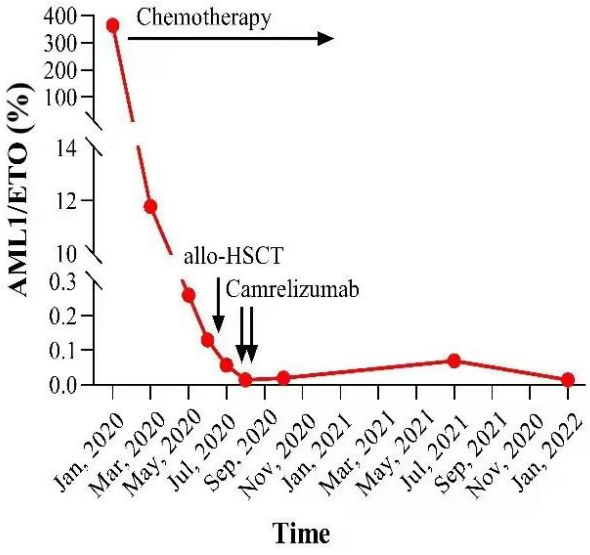

Figure 1. The transcripts of CBFβ-MYH11 in bone marrow of case 1 at indicated time points. Arrows indicated the time of chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), as well as camrelizumab.

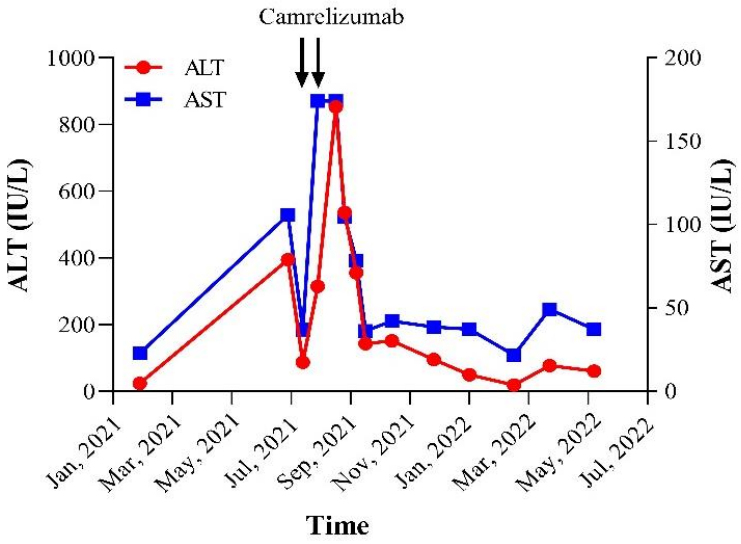

Figure 2. The levels of ALT (glutamic pyruvic transaminase) and AST (glutamic oxaloacetic transaminase) in case 1 measured before and after camrelizumab.

2.2. Case 2

A 20-year-old man was diagnosed favorable risk AML in January 2020. Cytogenetics revealed a t(8;21) (q22;q22) translocation generating a recurrent leukemia-specific fusion gene product AML1-ETO (364.65%, fusion transcript copies/ABL copies) (Figure 3). After a cycle of induction chemotherapy with homoharringtonine and cytarabine, the patient reached partial remission (PR). Then, the patient received two cycles of high dose cytarabine and reached continuous CR. However, molecular remission was not achieved, as the MRD of AML1-ETO transcripts remained at 0.069% (fusion transcript copies/ABL copies). Consequently, allo-HSCT was performed in June 2020. Two months after transplantation, the AML1-ETO transcript remained positive at 0.019% (fusion transcript copies/ABL copies). Subsequently, he received decitabine as a preemptive treatment, and the fusion transcript became negative. One year after transplantation, he experienced a molecular relapse with an MRD of AML1-ETO transcripts at 0.069% (fusion transcript copies/ABL copies) (Figure 3). Therefore, the patient was informed and prescribed 200 mg of camrelizumab for 2 cycles at every two-week interval. The AML1-ETO transcript in bone marrow decreased to 0.014% (fusion transcript copies/ABL copies) (Figure 3). However, the severe liver injury that occurred in this patient was most likely caused by irAEs associated with camrelizumab, which could not be continued in this patient. After steroid treatment, liver function improved gradually (Figure 4). The MRD and liver function were persistently normal on regularly follow-up.

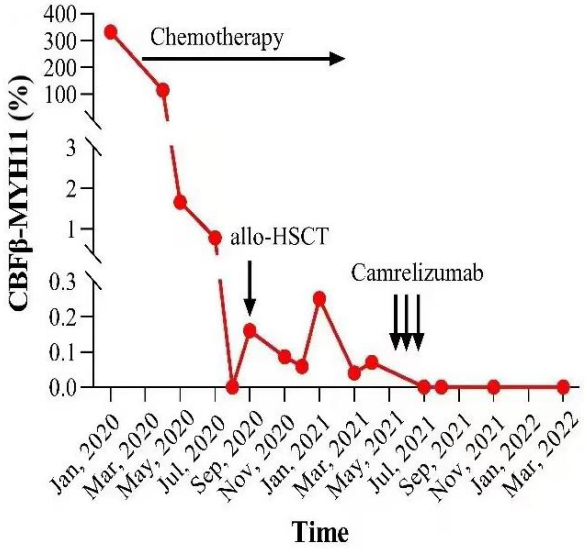

Figure 3. The transcripts of AML1-ETO in bone marrow of case 2 at indicated time points. Arrows indicated the time of chemotherapy, allogeneic hematopoietic stem cell transplantation (allo-HSCT), as well as camrelizumab.

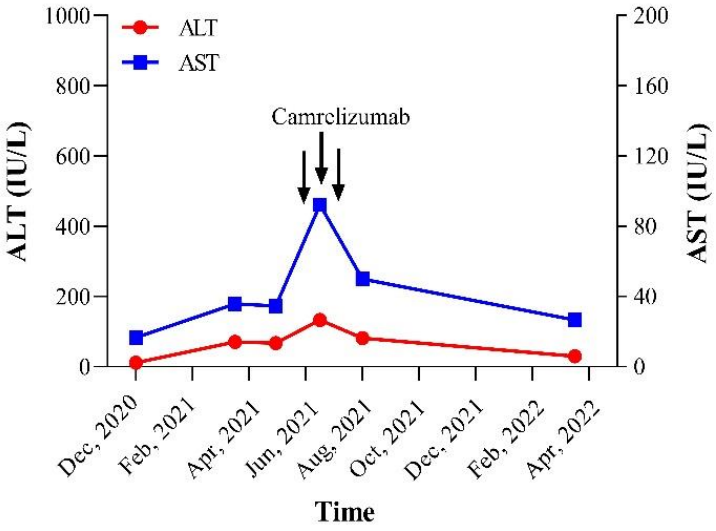

Figure 4. The levels of ALT (glutamic pyruvic transaminase) and AST (glutamic oxaloacetic transaminase) in case 2 measured before and after camrelizumab.

3. Discussion

Although AML cells are originated from an immune-rich bone marrow, they still destroy normal hematopoietic cells and immune cells, leading to immune escape. Therefore, allo-HSCT remains a good option for curing leukemia, primarily due to the GVL effect [9]. Regular MRD monitoring and preemptive treatment are particularly important to leukemia relapse prophylaxis [1]. In this study, we discussed the important role of camrelizumab, one of the immune checkpoint inhibitors, in managing molecular relapse of AML after allo-HSCT. In the two cases, camrelizumab was effective in the therapeutic intervention of molecular relapse post-allo-HSCT. However, irAEs need to be carefully identified and managed.

After allo-HSCT, leukemia relapse can be prevented by chemotherapy, targeted drugs, and donor lymphocyte infusion, usually guided by MRD status. In clinical practice, treatment options are limited for a variety of reasons, creating an urgent need for new approaches. After immune checkpoint inhibitors changed the prognosis of solid tumors [10–12], the pair of immunosuppressive molecules PD-1 and PD-L1 attracted much attention as targets of tumor immunosuppression. High PD-L1 expression on tumor cells and PD-1 expression on T cells leads to immune escape of tumor cells, which can be countered by blocking this pathway to achieve a therapeutic effect [13]. Similar to solid tumors, applications of immune checkpoint inhibitors for AML are being explored. Studies indicate that PD-1 is usually highly expressed on T cells in AML patients, suggesting an exhausted phenotype. PD-1 can also be induced in NK cells, B cells, and monocytes. DNA hypomethylating drugs can enhance the expression of PD-L1 in myelodysplastic syndrome (MDS). A large number of patients had a poor response to hypomethylating drugs, and the increased PD-L1 expression may be related to treatment resistance [14]. In addition, there is a higher expression of PD-1 in T cells of patients with refractory/recurrent AML [15]. In a clinical trial, 10 refractory/recurrent AML patients were enrolled and treated with a combination of pembrolizumab and decitabine, of which 6 patients achieved good efficacy [16]. A study combining azacitidine with nivolumab for refractory/recurrent AML found that the overall response rate (ORR) was 33%, indicating that azacitidine in combination with nivolumab appears to be an effective therapy for patients with refractory/recurrent AML [17]. In another phase 2 study, Zeidner et al. found that immune checkpoint blockade with pembrolizumab was tolerable and feasible after high-dose cytarabine in relapsed/refractory AML [18]. T cell exhausting is common in leukemia, and therapeutic monoclonal antibodies against PD-1 can decrease T cell exhaustion and restore its function [19]. According to many clinical data, PD-1 inhibition can enhance GVL effect. Combined with our two cases, preliminary results suggest that PD-1 blockade is an effective therapy for preemptive treatment of molecular relapse after allo-HSCT in AML.

Although PD-1 blockers achieve excellent results in current studies, they are still accompanied by an increased risk of immunotoxicity and may cause severe GVHD [20]. PD-1/PD-L1 inhibitors accelerate the amplification of donor $CD8^+$ T cells and aggravate GVHD [21]. Therefore, the conditioning regimen and the prevention of GVHD are particularly important. Meanwhile, the timing and dose of PD-1 inhibitors in preemptive treatment after transplantation

are still major challenges. A study on the use of PD-1 inhibitors after allo-HSCT for Hodgkin's lymphoma suggests that the drug appears to be safer for patients who relapse more than six months after transplantation. According to both mice and clinical data, it also indicates that the risk of early administration after transplantation is higher. In addition, the first use of PD-1 inhibitor started with a low dose. If there was no reaction and no toxicity, increasing the dose should be considered to obtain the maximum clinical benefit [22]. Therefore, PD-1 inhibitors can be used after allo-HSCT for preemptive treatment under certain safety conditions, but this conclusion still needs to be verified by large-scale studies.

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Author Contributions

L.Z. and S.L. obtained and analyzed the clinical data. Y.H. and S.Z. made the figures. The authors all contributed to caring for the patient, editing the figures, and writing and editing the manuscript. G.H. and H.Y. reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Ethics Statement

Involving human participants was approved by the Ethics Committee of the General Hospital of Western Theater Command, People's Liberation Army. All methods were carried out in accordance with the Declaration of Helsinki.

Informed Consent Statement

Patients provided written informed consent to participate in this study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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