CD7 CAR-T therapy for an AML patient with CD7 expression

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Abstract

To date, no ideal CAR-T product is available for treating acute myeloid leukemia (AML). Recently, CD7 CAR-T therapy has shown promising efficiency in treating T-cell acute lymphoblastic leukemia. Because the CD7 antigen is also expressed on the myeloid blasts of some patients with AML, it might serve as a target for immunotherapy in AML. Herein, we administered CD7-specific CAR-T cells into a 20-year-old woman with AML with CD7 expression. She had a history of multiple relapses (with extramedullary disease, EMD) and treatments (radiation and allogeneic hematopoietic cell transplantation). The most recent relapse indicated a high disease burden with multifocal EMD. After a combination regimen of azacytidine, venetoclax and ruxolitinib, she showed minimal residual disease-positive remission in the bone marrow (BM), and EMD remained present. Subsequently, donor-derived CD7 CAR-T cells infused at a dose of 5.5×10⁵/kg completely eliminated all disease in the BM and extramedullary areas. Grade I cytokine release syndrome occurred with no neurotoxicity. CD7 CAR-T cells were detectable in the peripheral blood and BM. Fifty-five days after T-cell infusion, she underwent a second allogeneic hematopoietic cell transplantation and has survived in disease-free remission for more than 7 months.

Keywords: CAR-T cell therapy, Acute myeloid leukemia, CD7

1. INTRODUCTION

CD19 or CD22 CAR-T cell therapy has shown remarkable results and has been widely used to treat relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (B-ALL) [1, 2]. Recently, CD7-specific CAR-T cells have also been found to increase complete remission (CR) rates (to 63.6%–90%) in patients with r/r T-cell acute lymphoblastic leukemia (T-ALL) [3, 4]. However, to date, no ideal CAR-T product is available for treating acute myeloid leukemia (AML), owing to the absence of an AML-specific antigen. AML cells express various cell surface antigens including CD123, CD34, CD33 and many others, which are shared by normal hematopoietic stem/progenitor cells and their myeloid and/or lymphoid progenitors. Only a few cases or case series have shown potential effects of CAR-T therapy against AML by targeting antigens such as CD123, CD44v6, Lewis Y, FLT3, CLL-1 or CD19 in patients with AML with CD19 expression [5-7].

The CD7 antigen is expressed in 31%–37% of patients with AML [8, 9]. A preclinical study in AML cell lines, primary CD7+ AML cells, and a mouse model has verified that CD7 CAR-T cells effectively eliminate CD7+ AML cells [10]. Very recently, two cases have been reported to achieve CR (one with minimal residual disease-positive CR, MRD+CR) after treatment with CD7 CAR-T cells [4, 11]. Here, we administered CD7-specific CAR-T cells into a post-transplantation patient with relapsed AML and extramedullary disease (EMD), and performed follow up to assess the treatment outcome.

This case study was approved by the Beijing Boren Hospital ethics committee, and informed consent was obtained.

2. PATIENT AND TREATMENTS

The patient’s disease history and treatments are summarized in Table 1. The patient was a 20-year-old woman diagnosed with AML (FAB-M5) in March 2017, with complex chromosomal karyotype 39–46, XX, t(1;11)(p36;q21), -10, add(10)(p13), -20, add(20)(p11)[cp20] and PHF6, TET2 and ASXL1 gene mutations. She achieved CR after one course of induction therapy (IDA+Ara-C),
then received another four courses of chemotherapy and remained in CR. In December 2017, she underwent allogeneic hematopoietic cell transplantation (allo-HCT) when her minimal residual disease was 0.23%, as detected by flow cytometry (FCM). In September 2018, she relapsed, with 16.5% myeloid blasts in the bone marrow (BM), and achieved CR2 after chemotherapy and donor lymphocyte infusions (DLI). Unfortunately, 1 year later, she relapsed again with EMD (without BM involvement), presenting with enlarged lymph nodes in the right regiones clavicularis, mediastinum and left axilla, as verified through lymph node biopsy. Local radiotherapy was administered to treat the EMD, and she achieved CR3.

In October 2021, diffuse disease reappeared in the lymph nodes and bones, and radiation treatment had no effect. Two months later, BM examination indicated that 66% of the nucleated cells were myeloid blasts. Interferon-γ was administered while the disease progressed. In January 2022, when the patient was admitted to our hospital, she presented with a high white blood cell count of 110.67×10⁹/L and more than 90% leukemia cells in the peripheral blood (PB) (Figure 1a-c), and still showed complex chromosomal karyotype 46,

**Table 1 | Summary of disease history and treatments.**

<table>
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<tr>
<th>Time</th>
<th>Disease status</th>
<th>Treatment and response</th>
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| Mar 2017 (at diagnosis) | WBC: 9.36×10⁹/L  
Blasts in BM: morphology 46.5%  
FCM 47.0% | IA (IDA+Ara-C)  
HD-Ara-C ×3  
IA | CR  
CR  
CR |
| Dec 2017            | BM: morphology CR  
FCM 0.23% blasts | Allo-HCT | CR |
| Sep 2018 (relapse)  | BM: morphology 16.5% blasts | (Chemotherapy+DLI) ×3 | CR2 |
| Sep 2019 (second relapse) | EMD (enlarged lymph nodes in right regiones clavicularis, mediastinum and left axilla), no BM involvement | Local radiotherapy | CR3 |
| Oct 2021 (third relapse) | Multifocal EMD, no BM involvement | Local radiotherapy | SD |
| Jan 2022 (at admission to our hospital) | WBC: 110.67×10⁹/L  
Blasts in PB: morphology 95%  
FCM 97.7%  
Multifocal EMD | Azacytidine+Venetoclax+Ruxolitinib | PR |
| Mar 2022            | EMD diminished but still present  
BM: MRD 0.48% (FCM) | CD7 CAR-T cells | CRi |
| May 2022            | BM: MRD-negative CR  
EMD: CR | Second allo-HCT | CR |

Abbreviations: WBC, white blood cell; BM, bone marrow; FCM, flow cytometry; CR, complete remission; allo-HCT, allogeneic hematopoietic cell transplantation; DLI, donor lymphocyte infusion; EMD, extramedullary disease; SD, stable disease; PB, peripheral blood; PR, partial remission; MRD, minimal residual disease; CRi, CR with incomplete blood count recovery.

**Figure 1 | Myeloid blasts in the patient’s peripheral blood after admission to our hospital.**
(a) Blast cells from a blood smear. (b) and (c) Red dots represent leukemia cells expressing the CD7 antigen, as assayed by flow cytometry.
XX, add (1) (p13), add (1) (p32), add (10) (p11. 2) del (11) (q21), add (16) (q21), -20, +22 and inc [cp10]. She discontinuously received a combination regimen of 100 mg azacytidine for 7 days, 50–300 mg venetoclax for 21 days and ruxolitinib for 12 days (a JAK3 gene mutation was found at the time), because of gingival bleeding, gross hematuria and infections. In March 2022, she achieved MRD+CR (FCM 0.48%) in the BM but still had multilocal EMD, on the basis of PET/CT (Figure 2a).

Given that the CD7 antigen was expressed on the patient’s leukemic cells (Figure 1c), and we had CD7 CARs available for treating patients with T-ALL, we planned to attempt treatment with CD7-specific CAR-T cells for this patient with AML. Informed consent was obtained after discussion with the patient and her family. Subsequently, donor cells from her father were collected and used to produce CAR-T cells, which were transduced with lentiviral vectors carrying CD7 CARs composed of CD3ζ and 4-1BB. IntraBlock technology was used in CD7 CARs to prevent CD7 cell surface expression and CAR-T cell fratricide [3]. Before cell infusion, 5-day azacytidine (100 mg) and venetoclax (100–200 mg) instead of fludarabine and cyclophosphamide were given as a pretreatment, and a total of 5.5×10^5/kg CD7 CAR-T cells were infused on March 22, 2022. From day 6 to day 11 after cell infusion, the patient had a fever with a peak temperature of 39.1°. Low-dose dexamethasone was administered for 2 days.

Figure 2 | Evaluation of extramedullary disease (EMD).
(a) Representative EMD before CD7 CAR-T therapy, detected by PET/CT. (b) MRI showed no EMD 1 month after CAR-T cell infusion. (c) No EMD (PET/CT images) were observed 2 months after the second allo-HCT.
for grade I cytokine release syndrome, and no neurotoxicity was observed.

CAR-T cell numbers were determined with FCM (Figure 3a). CAR-T cell expansion in the PB was observed on day 8, and the peak cell number was 7.88×10^7/L on day 11. CAR-T cells were detectable until day 35 (Figure 3b), and no further data are available since the patient underwent a second allo-HCT. Accordingly, normal CD7 positive T-cells in the PB completely disappeared with the CAR-T cell expansion by day 8 and were undetectable until day 35, thus indicating that CD7 CAR-T cells targeted CD7 positive T-cells as well. CAR-T cells were also detected in the patient’s BM.

Treatment response was evaluated 1 month after CAR-T cell infusion. The patient achieved MRD-negative CR with incomplete blood count recovery. EMD was eliminated, as detected by MRI examination (Figure 2b). Subsequently, on May 17, 2022, the patient underwent a second allo-HCT, which proceeded smoothly. Two months after transplantation, PET/CT showed no abnormal fluoro-deoxyglucose uptake, and all EMD had disappeared (Figure 2c). As of the end of October 2022, she had been in CR for more than 7 months since the CD7 CAR-T cell infusion.

3. DISCUSSION

With traditional therapies, acute myeloid leukemia is cured in only 35%–40% of adult patients 60 years of age or younger [12]. The prognosis of patients relapsing after allo-HCT is extremely poor, with a CR rate of less than 30% after treatments with chemotherapy, DLI, secondary allo-HCT or combinations thereof [13]. In recent years, CD19 or CD22 CAR-T cells have tremendously improved the outcomes of patients with r/r B-ALL, including those with relapse after allo-HCT [1, 2, 14]. CD7 CAR-T therapy has also been reported to achieve 63.6%–90% CR in patients with r/r T-ALL [3, 4].

The clinical trials of CAR-T therapy for patients with r/r AML are ongoing. Because the CD7 antigen is expressed on the myeloid blasts of some patients with AML [8, 9], CD7 CAR-T cells may be used for treating AML with CD7 expression.

The patient with AML reported herein had a history of multiple relapses and treatments, as well as EMD, and received allo-HCT. The most recent relapse indicated a high disease burden with multifocal EMD. After a combination treatment including azacytidine, venetoclax and ruxolitinib, the patient achieved MRD+CR in the BM, but EMD still persisted. Subsequent CD7 CAR-T cell treatment completely eliminated all disease, thus indicating that CD7 CAR-T therapy had treatment effects on leukemic cells not only in the BM but also in extramedullary areas in this patient with AML with CD7 expression. The CR before transplantation achieved through treatment with CD7 CAR-T cells provided a favorable factor for successful transplantation. CD7 CAR-T cells and the following second allo-HCT allowed the patient to survive in disease-free remission for more than 7 months, as of the last follow-up.

Because this patient had a lower disease burden before CAR-T, the procedure of CAR-T therapy went very well; she showed only grade I cytokine release syndrome and no neurotoxicity. CD7 CAR-T cells were detectable in the PB from day 8 through day 35 (after which point no further data are available). Simultaneously, CD7 positive T-cells remained negative, thus indicating that the CD7 CAR-T cells targeted and eliminated both CD7 positive AML cells and normal T-cells. CD7 positive T-cells in the BM recovered 1 month after allo-HCT, thereby demonstrating that allo-HCT restored the patient’s CD7 positive T-cells and consequently decreased the risk of infection.

In summary, CD7 CAR-T cell therapy showed promising efficiency in a patient with AML with multiple relapses and EMD, and thus may serve as a treatment option.
option for patients with r/r AML with CD7 expression, even those with EMD.

CONFLICTS OF INTEREST
We declare no conflicts of interest.

REFERENCES