Oncology and Translational Medicine
DOI 10.1007/s10330-020-0450-0

February 2021, Vol. 7, No. 1, P45–P47

CASE REPORT

Megakaryocyte aplastic thrombocytopenia after CAR T-cell therapy in a patient with multiple myeloma: A case report

Shangqin Liu (✉), Chengsi Gui

Department of Hematology, Zhongnan Hospital of Wuhan University, Wuhan 430071, China

Abstract

Chimeric antigen receptor (CAR) T-cell therapy is an effective new treatment strategy for hematologic malignancies. The success of CAR T-cell therapy in treating leukemia and lymphoma has promoted its development for multiple myeloma (MM), and the initial results of CAR T cell therapy have been encouraging. CAR T-cell therapy target antigens that have been clinically evaluated in MM; these antigens include CD19, B cell maturation antigen (BCMA), CD38, and CD138. A barrier to the widespread use of CAR T-cell therapy is its toxicity, primarily cytokine release syndrome (CRS), and neurologic toxicity. This study reports a patient with refractory MM who also developed megakaryocyte aplastic thrombocytopenia after receiving CAR T-cell therapy; such a case or the unusual side effects involving medications are yet unreported. There are risks in using cyclosporine and other immunosuppressants that may lead to MM recurrence as the use of such substances is contradictory to previous treatments; therefore, we temporarily administered platelet infusion as supportive care. Thus far, the condition of the patient has been steady and the patient regularly takes blood test in the hospital.

Received: 16 October 2020
Revised: 5 November 2020
Accepted: 25 November 2020

Key words: megakaryocyte aplastic thrombocytopenia; chimeric antigen receptor (CAR) T cell therapy; multiple myeloma; case report

A 51-year-old female sought treatment at Tongji Hospital in Wuhan in August 2018 after reportedly experiencing pain in her left lower back. Complete bone marrow aspiration was performed, and multiple myeloma (34.5% bone marrow plasma cells, 25.5% naïve plasma cells) was diagnosed; 13q14 deletion, IGH separation, and 1q21 amplification were identified using fluorescence in situ hybridization (FISH). Furthermore, immunoglobulin testing was performed, and an M protein level of 31.6 g/L (accounting for 34.2%) was recorded. Serum immunofixation electrophoresis indicated the presence of immunoglobulin A lambda lanes, and the level of serum-free light chain was 850 mg/L for lambda lanes. Later, the patient received three cycles of bortezomib, doxorubicin, and dexamethasone (PAD) chemotherapy and three cycles of bortezomib, lenalidomide, and dexamethasone (VRD) chemotherapy from August 2018 to January 2019. After chemotherapy, bone marrow aspiration was performed and indicated 4% bone marrow plasma cells, and MRD testing indicated that 0.62% of the nucleated cells were phenotypically abnormal monoclonal plasma cells.

In March 2019, the patient received one dose of 47 mg fludarabine for three days and one dose of 400 mg cyclophosphamide for three days prior to anti-BCMA and anti-CD38 CAR T cell infusion. Two weeks later, bone marrow aspiration indicated that the bone marrow hyperplasia was no longer active, and megakaryocytes were observed. MRD results indicated the absence of nucleated cells. Moreover, the immunoglobulin test indicated an M protein level of 0.8 g/L (accounting for 1.2%). CAR T-cell immunodetection indicated an increase in human IL-10 (7.13 pg/mL). Then, the patient was discharged. Furthermore, the blood of the patient was tested every three months. In March 2020, her blood test indicated thrombocytopenia. Subsequently, she was

✉ Correspondence to: Shangqin Liu. Email: ubeliu@aliyun.com

treated with Sheng platelet capsules, caffeic acid tablets, and platelet transfusion; however, no marked effects were noted. On May 13, 2020, she was admitted to our hospital.

Her physical examination results were normal, and her blood count was as follows: 3.79 × 10^9/L WBC, 3.04 × 10^{12}/L RBC ↓, 103 g/L HB ↓, 4 × 10^9/L PLT ↓, 101.60 fL ↑ MCV; her direct Coombs test results, COVID-19 antibody and platelet specificity, and tissue-associated fusion antibody test results were all normal. The immunoglobulin test indicated the disappearance of M protein. Bone marrow aspiration indicated morphological remission after MM treatment. Moreover, bone marrow hyperplasia was decreased, and granulocyte, mononuclear cell, and lymphocyte levels were normal; however, her megakaryocyte count was extremely low; only one was counted, and her platelet levels were also low.

Currently, our diagnosis of the disease is megakaryocyte aplastic thrombocytopenia, which might have resulted from CAR-T treatment. As for the treatments, we transitorily provided treatment for hemostasis by infusing platelets; thus far, the patient's condition has remained stable.

Discussion

CAR T-cell therapy is an effective new treatment for hematologic malignancies. CARs are proteins that incorporate an antigen recognition domain and T cell signaling region. After gene modification, CARs expressed by T cells can specifically recognize and eliminate malignant cells that express the target antigens. The target antigens must be expressed on MM cells; importantly, they must be absent or restricted to healthy tissues. CAR T-cell therapy targets antigens that have been clinically evaluated in MM; these antigens include CD19, B cell maturation antigen (BCMA), CD38, and CD138. BCMA is a tumor necrosis factor (TNF) receptor superfamily 17 (TNFRSF17) that plays a central role in regulating B cell maturation and differentiation into plasma cells (PC).

Therefore, BCMA is an excellent target owing to its preferential expression in plasma cells [1]. Trial reports have indicated that BCMA CAR T therapy has strong effects in relapsed or refractory MM and can induce complete tumor remission [1–2]. CD38 is a multifunctional cell surface protein that has receptor and enzymatic functions. It is consistently expressed on malignant plasma cells, making it a suitable target for CAR T cell therapy. Moreover, it is generally expressed at low levels in various hematological and solid tissues. Altogether, this triggered the development of various therapeutic CD38 antibodies, and early clinical data show a marked activity in MM; however, the potential of CAR T cells does not guarantee safety when targeting widely expressed proteins [3–5].

Multiple hematologic toxicities may occur following CAR T cell infusions [2, 6]. In previous trials, most cytopenia cases occurred early after CAR T cell infusion and were attributable to cyclophosphamide and fludarabine conditioning chemotherapy [7]; however, the periods of some cytopenia cases can last for prolonged periods. In this case, the patient continued to experience cytopenia and platelet crisis one year after receiving CAR T-cell therapy. Based on bone marrow aspiration result, we considered that bone marrow was depressed by cyclophosphamide and fludarabine conditioning chemotherapy, and megakaryocyte aplastic may be due to CAR T cell therapy targeting megakaryocyte precursor cells; however, the underlying mechanisms remain unclear.

As there are risks in using cyclosporine and other immunosuppressants that may lead to MM recurrence, we temporarily administered platelet infusions for support care as we waited for the CAR T cells to be expended, and observed whether blood cells would gradually return to normal.

CAR T-cell therapy is an effective new treatment strategy for hematologic malignancies. It is still being tested in clinical trials, and the initial results have been encouraging. CAR T-cell therapy remains relatively new and the management of CAR T-cell toxicities is in early stage. Further animal experiments are needed to assess different immunosuppressive thresholds and to determine whether immunosuppressants can be used, whether they have an impact on clinical long-term remission, and when they are appropriate for use.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Sellner L, Fan F, Giesen N, *et al*. B-cell maturation antigen-specific chimeric antigen receptor T cells for multiple myeloma: clinical experience and future perspectives. Int J Cancer, 2020, 147: 2029–2041.
2. Ali SA, Shi V, Maric I, *et al*. T cells expressing an anti–B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. Blood, 2016, 128: 1688–1700.
3. Ghosh A, Mailankody S, Giralt SA, *et al*. CAR T cell therapy for multiple myeloma: where are we now and where are we headed? Leuk Lymphoma, 2018, 59: 2056–2067.
4. Grywalska E, Sosnowska-Pasiarska B, Smok-Kalwat J, *et al*. Paving the way toward successful multiple myeloma treatment: chimeric antigen receptor T-cell therapy. Cells, 2020, 9: 983.
5. van de Donk NW, Janmaat ML, Mutis T, Lammerts VBJ, *et al*. Monoclonal antibodies targeting CD38 in hematological malignancies and beyond. Immunol Rev, 2016, 270: 95–112.
6. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev, 2019, 34: 45–55.

7. Brudno JN, Maric I, Hartman SD, *et al*. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol, 2018, 36: 2267–2280.

DOI 10.1007/s10330-020-0450-0
Cite this article as: Liu SQ, Gui SC. Megakaryocyte aplastic thrombocytopenia after CAR T-cell therapy in a patient with multiple myeloma: A case report. Oncol Transl Med, 2021, 7: 45–47.