Regenerative Therapy 14 (2020) 271–274

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Letter to the editor

Idiopathic thrombocytopenic purpura treatment in a relapsed/refractory multiple myeloma patient after chimeric antigen receptor T cell therapy

Keywords:
Idiopathic thrombocytopenic purpura
Chimeric antigen receptor T cells
B cell maturation antigen
Relapsed/refractory multiple myeloma
BCMA CAR-T therapy

A B S T R A C T

The adoptive transfer of CAR-T cells, which are modified T cells expressing chimeric antigen receptors (CARs), to target B cell maturation antigen (BCMA) has demonstrated impressive results in treating relapsed/refractory multiple myeloma. Although BCMA CAR-T therapy induces certain complications in some patients, idiopathic thrombocytopenic purpura (ITP) has not been reported as one of them. To the best of our knowledge, this is the first report of the successful treatment of ITP that arose in a relapsed/refractory multiple myeloma patient following anti-BCMA CAR-T cell infusion. Herein, we describe this relatively uncommon complication and provide guidance on its treatment.

1. Introduction

Chimeric antigen receptor T cells (CAR-Ts) have recently been shown to improve treatment outcomes for B cell malignancies. High complete remission (CR) rates have been reported in several independent clinical trials of CAR-T treatment [1–7]. Recent studies have identified unique toxicities associated with CAR-T therapy, including cytokine release syndrome (CRS) and CAR-T-related encephalopathy syndrome [8–13]; however, cases of delayed idiopathic thrombocytopenic purpura (ITP) after CAR-T therapy have not been reported. We are the first to describe a case of successfully treated ITP that had been induced by CAR-T therapy in a relapsed/refractory multiple myeloma patient.

2. Case

A 50-year-old male was diagnosed with IgD lambda multiple myeloma in July 2016 after presenting with anemia and chest pain. Induction therapy with one cycle of bortezomib, cyclophosphamide, and dexamethasone resulted in a partial response. He then received four cycles of bortezomib, lenalidomide, and dexamethasone and achieved a very good partial response, which was consolidated with autologous stem cell transplantation. Approximately 9 months later, the disease relapsed, and the patient was treated with one cycle of ixazomib, lenalidomide, and dexamethasone and three cycles of ixazomib, pomalidomide, and dexamethasone. However, the decrease in serum M-protein was only temporary. In 2018, the patient consented to participate in a clinical trial (ChiCTR–OIC–17011310) of anti-B cell maturation antigen (BCMA) CAR-T treatment. The patient provided written, informed consent, which included hematologic toxicity. On December 19, after lymphodepletion chemotherapy with fludarabine and cyclophosphamide, he was infused with 5.85×10^6/kg of autologous T cells expressing an anti-BCMA-CAR construct (Fig. 1).

Within 24 h of infusion, the patient developed a high fever of up to 40 °C (Fig. 2C) and pancytopenia along with extremely elevated levels of serum C-reactive protein, D-dimer, interleukin (IL)-6, IL-10, and ferritin (Fig. 2B, D). Consequently, grade I CRS was diagnosed [14]. His body temperature and white blood cell count returned to normal after 20 days, but the platelet count was low for over 1 month, necessitating frequent platelet transfusions (Fig. 2A). On January 23, 2019, the patient was discharged from the hospital with a platelet count of 23×10^9/L. Assessment of his bone marrow aspirate by flow cytometry revealed that plasma cells were undetectable. Moreover, serum and urine M-protein assays were negative, indicating that the patient was in CR. His platelet count normalized 3 months after hospital discharge.

On July 20, 2019, the patient presented with skin ecchymosis, without fever, fatigue, or pain. His platelet count had decreased to 1×10^9/L, whereas the white blood cell count and hemoglobin level were normal. Bone marrow aspiration showed an absence of thrombogenic megakaryocytes (Fig. 3). Tests for antinuclear and antiphospholipid antibodies and hepatitis B and C were all negative. Secondary causes of thrombocytopenia, such as autoimmune diseases, lymphatic proliferative disease, bone marrow failure

Abbreviations: BCMA, B cell maturation antigen; CAR-Ts, chimeric antigen receptor T cells; CARS, chimeric antigen receptors; CR, complete remission; CRS, cytokine release syndrome; ITP, idiopathic thrombocytopenic purpura.

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2020.03.005

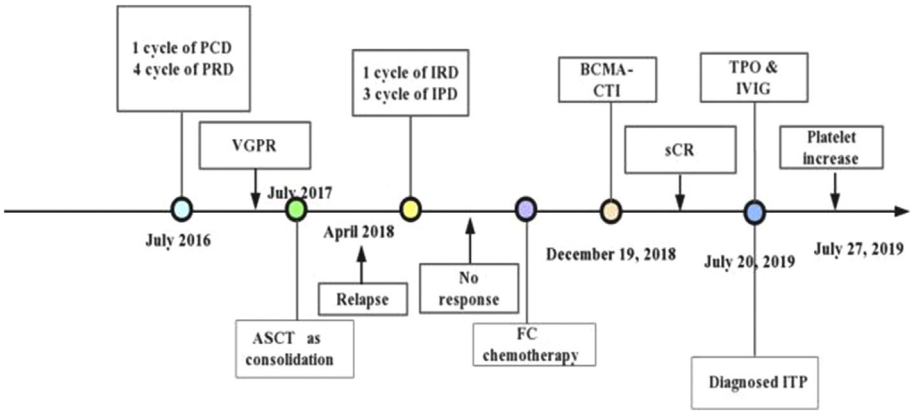

Fig. 1. Flow chart of the patient's treatment.

disorders, hematological malignancies, hypersplenism, and infection, were excluded. Due to bleeding symptoms and low platelet levels, the patient was treated at the local hospital, and data for other tests such as measurements of thrombopoietin and reticulated platelets were incomplete. Multiple myeloma was still in CR, as demonstrated by the absence of serum M-protein. The patient was treated with recombinant human thrombopoietin (15,000 U/day) and immunoglobulin (400 mg/kg/day) for 5 days. Glucocorticoids were not administered because the patient had undergone BCMA CAR-T therapy. The platelet count increased to 75 $\times$ 10^9/L after 7 days of treatment (Fig. 3). Laboratory tests at the local hospital and successful treatment supported the diagnosis of ITP. One year after CAR-T therapy, the patient's multiple myeloma remained in CR without a relapse of ITP.

3. Discussion

We are the first to report a case of ITP that arose in a patient with relapsed/refractory multiple myeloma after BCMA CAR-T therapy. The case was successfully treated with recombinant human thrombopoietin and immunoglobulin and without glucocorticoids. Thrombocytopenia is a clinical manifestation of CAR-T cell toxicity.

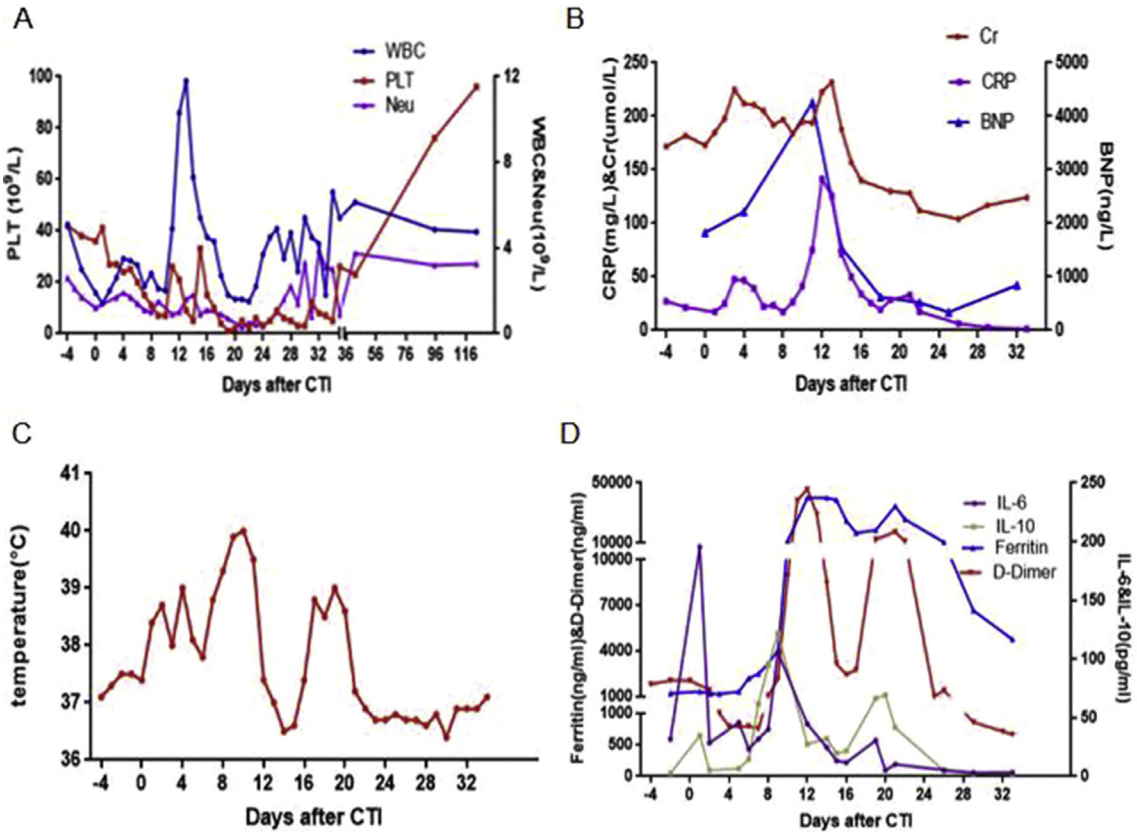

Fig. 2. Clinical course after B cell maturation antigen chimeric antigen receptor T cell (BCMA CAR-T) therapy. (A) White blood cell (WBC), neutrophil (NEU), and platelet (PLT) counts decreased after Car-T treatment. The former returned to a normal level after 1 month, whereas the latter took over 3 months to normalize. (B) Serum C-reactive protein (CRP), B-type natriuretic peptide (BNP), and creatinine (Cr) concentrations increased after Car-T treatment, then returned to normal levels. (C) The body temperature increased after Car-T treatment, then returned to normal. (D) Serum levels of interleukin (IL)-6, IL-10, ferritin, and D-dimer were elevated after Car-T treatment, then returned to normal levels.

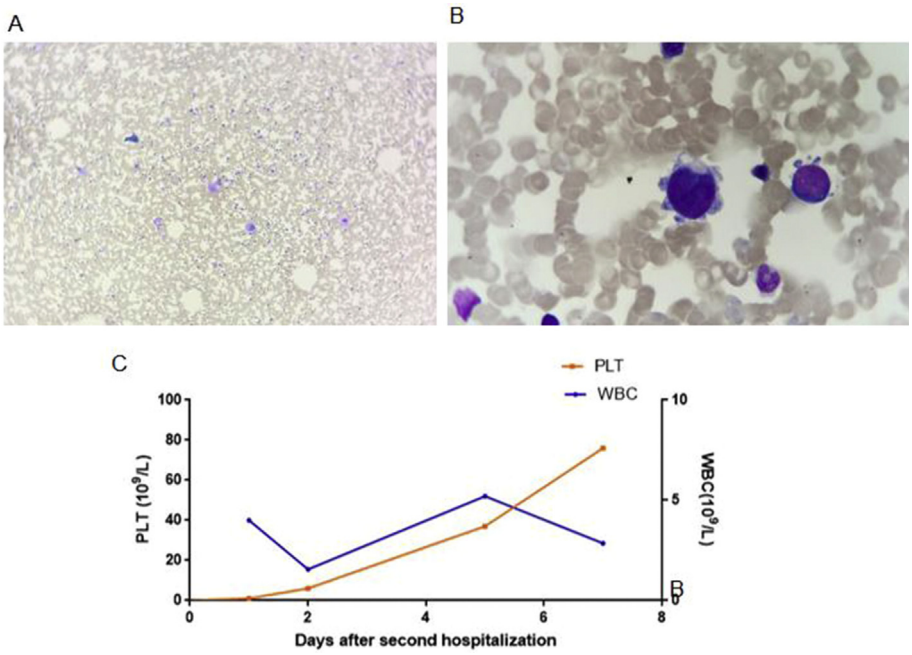

Fig. 3. Bone marrow and platelet count analyses. (a, b) Light microscopic images of a Wright's stained bone marrow aspirate of the patient before thrombopoietin and immunoglobulin treatment (10× and 100×, respectively). (c) Changes to the patient's platelet count after thrombopoietin and immunoglobulin treatment during the second hospitalization.

Although conditioning chemotherapy regimens are known to contribute to the development of thrombocytopenia, Brudno et al. [15] reported that in patients with high disease burdens, anti-CD19 CAR-T cells administered without chemotherapy could still cause cytopenia. Ali et al. [16] reported that a patient with multiple myeloma experienced prolonged thrombocytopenia following BCMA CAR-T treatment. The authors proposed that high levels of cytokines, which are produced when anti-BCMA CAR T cells encounter a high multiple myeloma burden, and the bystander perforin/granzyme-mediated killing of hematopoietic cells might explain the observed effect. These mechanisms might have induced thrombocytopenia during our patient's first hospitalization. However, in contrast to that observed in our case, the patient reported by Ali et al. recovered 8 weeks after CAR-T cell infusion and showed no evidence of thrombocytopenia at follow-up.

In our study, the patient presented with ITP 7 months after BCMA CAR-T therapy, even though his platelet count had normalized 4 months earlier. Fried et al. [17] reported late hematologic toxicity in 38 patients following CD19 CAR-T cell administration. They assumed that thrombocytopenia arises from two distinct mechanisms; the first event occurs following lymphodepleting therapy, whereas the second event seems unrelated to this. There may or may not be an interim recovery between these two phases. Of the patients treated with axicabtagene and ciloleucel for lymphoma, 7% had thrombocytopenia 3 months following the infusion [18]. These reports are consistent with our case and further support the diagnosis of ITP. The patient had transient leukopenia in the later stage, considering the late hematological toxicity.

Although immune checkpoint inhibitors [19] and vaccines [20,21] can cause ITP, the pathophysiology of ITP is not fully understood. Molecular mimicry and/or immune provocation by specific antigen exposure that induces an autoimmune response against platelets in susceptible individuals might underlie the development of ITP [22]. Until more data become available, patients receiving BCMA CAR-T therapy should be monitored for signs of ITP at follow-up.

The use of corticosteroids might impair the anti-leukemia function of CAR-T cells through the inhibition of T cell activation, resulting in attenuation of the therapeutic effect. In our case, we treated the patient with 15,000 U/day of recombinant human thrombopoietin and 400 mg/kg/day of immunoglobulin for 5 days. This regimen restored the platelet count to a normal level with no evidence of ITP relapse at 1-year follow-up. The present report raises awareness of delayed ITP as a complication of anti-BCMA CAR-T cell infusion and offers guidance to aid its diagnosis and treatment without compromising the therapeutic effect of CAR-T cell therapy. However, more extensive studies are needed to clarify the underlying pathophysiological mechanisms.

Funding

This work was supported by the 973 Program under grant number 2015CB964900; the Natural Science Foundation of China under grant numbers 81470341, 81770201, and 81730008; the Key Project of Science and Technology Department of Zhejiang Province under grant numbers 2018C03016-2 and 2015C03G2150011; and the Zhejiang Public Welfare Foundation under grant number GF18H180002.

Informed consent

The patient provided written consent for the inclusion of material pertaining to himself, and he understood that he was fully anonymized and could not be identified via this report.

Declaration of competing interest

None.

References

[1] Frey NV, Porter DL. The promise of chimeric antigen receptor T-cell therapy. Oncology (Williston Park) 2016;30:880–8.
[2] Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med 2018;378:449–59.
[3] Hu Y, Wu Z, Luo Y, Shi J, Yu J, Pu C, et al. Potent anti-leukemia activities of chimeric antigen receptor-modified T cells against CD19 in Chinese patients with relapsed/refractory acute lymphocytic leukemia. Clin Canc Res 2017;23:3297–306.
[4] Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, et al. 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;36:2267–80.
[5] June CH, Sadelain M. Chimeric antigen receptor therapy. N Engl J Med 2018;379:64–73.
[6] Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517–28.
[7] Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood 2017;129:3322–31.
[8] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531–44.
[9] Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. Canc Discov 2017;7:1404–19.
[10] Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biologic correlates of neurotoxicity associated with CAR T cell therapy in patients with B-cell acute lymphoblastic leukemia (B-ALL). Canc Discov 2018;8:958–71.
[11] Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor modified T-cell therapy. Blood 2017;130:2295–306.
[12] Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321–30.
[13] Jin A, Feng J, Wang Z, Jiang L, Hu Y, Zhao K, et al. Severe dyspnea caused by rapid enlargement of cervical lymph node in a relapsed/refractory B-cell lymphoma patient following chimeric antigen receptor T-cell therapy. Bone Marrow Transplant 2019;54:969–72.
[14] Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. How I treat: current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188–95.
[15] Brudno JN, Somerville RP, Shi V, Rose JJ, Halverson DC, Fowler DH, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. J Clin Oncol 2016;34:1112–21.
[16] Ali SA, Shi V, Maric I, Wang M, Stroncek DF, Rose JJ, et al. T cells expressing an anti-B-cell maturation antigenchimeric antigen receptor cause remissions of multiple myeloma. Blood 2016;128:1688–700. 17.1窗体底端.
[17] Fried S, Avigdor A, Bielorai B, Meir A, Besser MJ, Schachter J, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant 2019;54:1643–50.
[18] Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and efficacy of axicabtagene ciloleucel in refractory large B-cell lymphoma: a multicenter, single arm, phase 1–2 trial. Lancet Oncol 2018;20:31–42.
[19] Shiuan E, Beckermann KE, Ozgun A, Kelly C, McKean M, McQuade J, et al. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. J Immunother Canc 2017;5:8.
[20] Bizjak M, Bruck O, Kanduc D, Praprotnik S, Shoenfeld Y. Vaccinations and secondary immune thrombocytopenia with antiphospholipid antibodies by human papillomavirus vaccine. Semin Hematol 2016;53(Suppl 1):S48–50.
[21] Owatanapanich S, Wanlapakorn N, Tangsiri R, Poovorawan Y. Measles-mumps-rubella vaccination induced thrombocytopenia: a case report and review of the literature. Southeast Asian J Trop Med Publ Health 2014;45:1053–7.
[22] Johnsen J. Pathogenesis in immune thrombocytopenia: new insights. Hematol Am Soc Hematol Educ Progr 2012;2012:306–12.

Lei Qiu[1], Feng Zhu[1]
Department of Hematology, Zhoushan Hospital, Zhoushan, 310000, China

Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310000, China

Guoqing Wei, Wenjun Wu, Luxin Yang, Yongxian Hu, He Huang[*]
Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310000, China

Zhejiang Province Engineering Laboratory for Stem Cell and Immunity Therapy, Hangzhou, 310000, China

Institute of Hematology, Zhejiang University, Hangzhou, 310000, China

[*] Corresponding author. Bone Marrow Transplantation Center, The First Affiliated Hospital, School of Medicine, Zhejiang University, No. 79 Qingchun Road, Hangzhou, China, Telephone and fax: 86-0571-87236706.
E-mail addresses: huyongxian2000@aliyun.com (Y. Hu), huanghe@zju.edu.cn (H. Huang).

3 February 2020