Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

Anti-BCMA CAR-T Administration in a Relapsed and Refractory Multiple Myeloma Patient after COVID-19 Infection

Madduri D[1]*, Parekh S[1], Campbell TB[2], Neumann F[3], Petrocca F[3] and Jagannath S[1]

[1]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, USA

[2]Bristol-Myers Squibb, Princeton, USA

[3]Bluebird bio, Cambridge, MA, USA

***Corresponding author:** Madduri D, Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Pl Box 1185, NY 10029, New York, USA

Received: August 15, 2020; **Accepted:** September 09, 2020; **Published:** September 16, 2020

Abstract

Very little is known about the risk that SARS-CoV-2 viral infection poses to cancer patients, many of whom are immune compromised. As a precautionary measure, many clinical studies halted enrollment during the initial surge of the global COVID-19 pandemic. Here we detail the successful treatment of a relapsed and refractory multiple myeloma patient treated with an anti-BCMA CAR T cell therapy immediately following clinical recovery from COVID-19. Although this patient had a history of immunosuppression and received one dose of lymphodepleting chemotherapy the day prior to COVID-19 diagnosis, this patient was able to mount a substantial immune response against the SARS-CoV-2 virus and antiviral antibodies remain detectable 2 months after receiving anti-BCMA CAR T cell therapy. Importantly, the recent SARS-CoV-2 infection in this patient did not exacerbate CAR T associated cytokine release syndrome and conversely the CAR T cell therapy did not result in COVID-19 related complications. As the COVID-19 global pandemic continues, the decision of whether to proceed with CAR T cell therapy will require extensive discussion weighing the potential risks and benefits of therapy, this case suggests that it is possible to successfully complete anti-BCMA CAR T cell therapy after recovery from COVID-19.

Abbreviations

ANC: Absolute Neutrophil Count; BCMA: B-Cell Maturation Antigen; CAR: Chimeric Antigen Receptor; CRP: C Reactive Protein; CRS: Cytokine Release Syndrome; IFN: Interferon; IL: Interleukin; IMWG: International Myeloma Working Group; Hb: Hemoglobin; κLC: Kappa Light Chain; LDC: Lymphodepleting Chemotherapy; Lym: Lymphocytes; MM: Multiple Myeloma; Tmax: Temperature; TNF: Tumor Necrosis Factor; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; WBC: White Blood Cell

Introduction

The global COVID-19 pandemic represents a worldwide public health crisis and directly impacts cancer care. Patients with Multiple Myeloma (MM) have cellular and humoral immune dysfunction causing them to be more susceptible to infections [1,2]. Anti-B Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T cell therapy is emerging as a promising option for relapsed myeloma patients, however most clinical trials of CAR-T therapy for MM were paused during the pandemic due to the possibility of increased morbidity and mortality with COVID. Specifically in MM patients, it is unclear whether the immunosuppression resulting from conditioning regimens used with CAR-T cell therapy may pose an increased risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition, COVID-19 may trigger an inflammatory cascade [3-5]. Similar to the Cytokine Release Syndrome (CRS) seen in some patients treated with CAR T cells [6]. Our experience in MM patients with COVID-19 showed they have a similar mortality when compared to the general age-matched COVID-19 infected population [7]. Our practice has therefore been to weigh the risks and benefits of treatment to tailor therapy for individual MM patients during the COVID-19 pandemic. Here we report the first case of a MM patient safely treated with anti-BCMA CAR T cell therapy immediately after clinical recovery from COVID-19.

Case Presentation

A 57-year-old male patient with a 4-year history of IgG Kappa MM was referred to Mount Sinai hospital in New York City in early February 2020 due to disease progression. He was penta-refractory (refractory to two proteasome inhibitors, two immunomodulatory agents, and an anti-CD38 antibody) and previously received 9 lines of therapy.

In early February of 2020, approximately 3.5 weeks prior to the first confirmed case of COVID-19 in New York City, the patient was enrolled in a clinical study (NCT03274219) of bb21217, an investigational BCMA directed CAR T cell therapy. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice and local or independent institutional review boards at each study center approved the protocol. The patient received bridging therapy with melphalan and bortezomib while awaiting CAR T cell manufacturing. He was asymptomatic and screened negative for SARS-CoV-2 before starting a planned three-day course of Lymphodepleting Chemotherapy (LDC). Approximately 24 hours after receiving the first dose of LDC [cyclophosphamide (300 mg/m^2) /fludarabine (30 mg/m^2)], the patient returned to clinic with fever, cough, and diarrhea. Nasopharyngeal PCR test confirmed SARS-

Citation: Madduri D, Parekh S, Campbell TB, Neumann F, Petrocca F and Jagannath S. Anti-BCMA CAR-T Administration in a Relapsed and Refractory Multiple Myeloma Patient after COVID-19 Infection. Ann Hematol Oncol. 2020; 7(7): 1311.

CoV-2 infection.

CAR-T infusion was held in the setting of active COVID-19 infection and the patient was admitted to the hospital for observation. He was afebrile upon admission with a mild cough that resolved within one day. He was given G-CSF for grade 1 neutropenia and discharged with instructions to self-isolate at home after 3 days of hospitalization.

The patient was monitored weekly and further therapy was held until SARS-CoV-2 clearance, which was confirmed 39 days after COVID-19 diagnosis. Upon approval by the Sponsor and our Institutional Review Board (IRB) the patient reinitiated the full three-day course of LDC in preparation for CAR T cell administration. At this point, inflammatory markers were normal and SARS-CoV-2 antibodies were detected at a titer of 1:2880 using an IgG assay developed by Mount Sinai [8]. On the day of CAR T cell infusion, lymphocytes in the peripheral blood were undetectable and the patient showed profound leukopenia. Twelve hours after CAR T cell infusion, clinical signs consistent with Grade 1 CRS developed, including fever and tachycardia [9]. On day 2, CRS escalated to Grade 2 and was accompanied by hypotension (81/52), only transiently responsive to fluids, thus tocilizumab (8 mg/kg) x 1 was given. The patient experienced 2 more days of low-grade fever, and grade 1 hypotension. CRS resolved by day 6 and cytokines returned to pretreatment levels by day 9. Blood counts improved by day 12 except lymphopenia which persisted through day 14. Based on 1-month follow-up post-CAR T cell infusion, the patient did not experience other complications, remained SARS-CoV-2 negative, and showed normalization of free kappa light chain with a 61% decrease in serum M protein, consistent with partial response per International Myeloma Working Group (IMWG) criteria. Repeat SARS-CoV-2 antibody titer at his 1-month follow up was 1:960 and 2-month follow up was 1:320.

Discussion/Conclusions

In this case report, we share the experience of successfully administering CAR T cell treatment in a relapsed and refractory multiple myeloma patient who recently recovered from COVID-19. Importantly, the administration of one day of LDC immediately prior to SARS-CoV-2 infection did not result in any COVID-19-related complications.

The patient experienced Grade 2 CRS, an expected toxicity associated with CAR T therapy, which resolved within 6 days and the patient is currently in partial response (unconfirmed), per IMWG assessment [10,11]. Inflammatory cytokines were elevated during the CRS event, however levels were in the same range as for CAR-T cell treated patients without COVID-19 who experience CRS [12]. Hence, recent SARS-CoV-2 infection in this patient did not exacerbate CAR T associated CRS, even though this is a toxicity known to be associated with COVID-19.

Interestingly, this patient experienced a robust humoral response to viral infection, despite his history of immune suppression. Two months after treatment with a BCMA directed CAR T therapy, which can ablate normal BCMA expressing plasma cells, the antibody titer decreased from 1:2880 to 1:320 but remained clearly detectable approximately 4 months after infection. Whether this patient developed and retained long-term immunity against COVID-19 remains to be determined.

With the initial surge of COVID-19, many clinical trial sites paused trials of CAR-T therapy for MM patients. As trials re-start, investigational sites should ensure access to critical care and availability of appropriate drugs to manage CAR T cell associated toxicities. Our report suggests that patients who have tested antibody positive for SARS-CoV-2 can proceed with CAR-T cell therapy without flare up of COVID 19 related symptoms. High antibody titers can be generated in myeloma patients [7], SARS-Cov-2 specific antibodies were retained despite effective anti-BCMA CAR T cell therapy in this patient. Additional studies to determine the effect of BCMA targeting agents on the risk of SARS-Cov-2 re-infection are warranted. As COVID-19 immunity after recovery has not been well characterized, appropriate precautions such as social distancing, facial mask, and good hygiene are recommended to prevent re-infection.

Acknowledgements

We would like to acknowledge all the staff and families for the selfless efforts in caring for patients who developed COVID-19, and the strength and courage of all patients affected by the pandemic.

Medical writing assistance was provided by Karen Repetny Ph.D., of bluebird bio, Cambridge, MA, USA.

References

1. Kumar SK, Anderson KC. Immune Therapies in Multiple Myeloma. Clin Cancer Res. 2016; 22: 5453-5460.
2. Lee SJ, Borrello I. Role of the Immune Response in Disease Progression and Therapy in Multiple Myeloma. Cancer Treat Res. 2016; 169: 207-225.
3. Ingraham NE, Lotfi-Emran S, Thielen BK, Techar K, Morris RS, Holtan SG, et al. Immunomodulation in COVID-19. Lancet Respir Med. 2020; 8: 544-546.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395: 1033-1034.
5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020; 20: 355-362.
6. Liu D, Zhao J. Cytokine release syndrome: grading, modeling, and new therapy. J Hematol Oncol. 2018; 11: 121.
7. Wang B, Van Oekelen O, Mouhieddine TH, Del Valle DM, Richter J, Cho HJ, et al. A tertiary center experience of multiple myeloma patients with COVID-19: lessons learned and the path forward. J Hematol Oncol. 2020; 13: 94.
8. Amanat F, Stadlbauer D, Strohmeier S, Nguyen THO, Chromikova V, McMahon M, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med. 2020; 26: 1033-1036.
9. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014; 124: 188-195.
10. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2019; 380: 1726-1737.
11. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467-1473.
12. Yi Lin JB, Noopur Raje, Nikhil Munshi, David Siegel, Michaela Liedtke, Sundar Jagannath, et al. First-in-human multicenter study of bb2121 anti-bcma car t cell therapy for relapsed/refractory multiple myeloma: Updated results. Eha Library. 2017.