Allogeneic CD34+ Selected Hematopoietic Stem Cell Boost Following CAR T-cell Therapy in a Patient with Prolonged Cytopenia and Active Infection

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Abstract

Hematological toxicity (hematotoxicity) is the most common long-term adverse effect following the use of CD19-chimeric antigen receptor (CD19-CAR) T-cell therapies. However, its management remains unclear. We present the case of a 21-year-old who received CD19-CAR T-cell therapy for relapse following a haploidentical transplant. He developed hematotoxicity and consequently multiple life-threatening infections. We administered a CD34+ hematopoietic stem cell boost (HSCB) from his transplant donor that led to hematopoietic recovery and resolution of his infections without any effect on the activity of CD19-CAR T cells. CD34+ HSCB can be a safe and effective option to treat hematotoxicity following CD19-CAR T-cell therapy.

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Abbreviations

Acute Lymphoblastic Leukemia	ALL
B-cell aplasia	BCA
bone marrow	BM
complete remission	CR
CD19-chimeric antigen receptor	CD19-CAR
cytokine-release syndrome	CRS
graft-versus- host-disease	GVHD
Hematological toxicity	hematotoxicity
hematopoietic stem cell boost	HSCB
hematopoietic stem cell transplant	HSCT
immune effector cell–associated neurotoxicity syndrome	ICANS
intensive care unit	ICU
lymphodepleting	LD

Abstract

Hematological toxicity (hematotoxicity) is the most common long-term adverse effect following the use of CD19-chimeric antigen receptor (CD19-CAR) T-cell therapies. However, its management remains unclear. We present the case of a 21-year-old who received CD19-CAR T-cell therapy for relapse following a haploidentical transplant. He developed hematotoxicity and consequently multiple life-threatening infections. We administered a CD34+ hematopoietic stem cell boost (HSCB) from his transplant donor that led to hematopoietic recovery and resolution of his infections without any effect on the activity of CD19-CAR T cells. CD34+ HSCB can be a safe and effective option to treat hematotoxicity following CD19-CAR T-cell therapy.

Manuscript

The use of CD19-specific chimeric antigen receptor (CD19-CAR) T-cell therapies has improved outcomes in patients with relapsed or refractory Acute Lymphoblastic Leukemia (ALL) (1). Their use is associated with a unique toxicity profile, including cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). These are treatment specific, immune-related adverse events and detailed and tailored management protocols have been established (2). However, real-world clinical experience has shown that hematological toxicity (hematotoxicity) is the most common long-term adverse event (3). The underlying pathophysiologic mechanism of hematotoxicity and its optimal management remain unclear.

Here we present the case of a 21-year-old man with B-ALL who developed hematotoxicity and severe life-threatening infections following CD19-CAR T-cell therapy and required a CD34+ hematopoietic stem cell boost (HSCB). He was initially diagnosed with B-cell ALL with IGH rearrangement and received remission induction therapy with CALGB10403. He had persistent disease at day 29 bone marrow (BM) evaluation and due to his high-risk disease status, proceeded to a myeloablative haplo-identical hematopoietic stem cell transplant (HSCT) utilizing a sibling donor. He relapsed nine months following HSCT with >90% CD19+ leukemic blasts by flow cytometry and received salvage chemotherapy with minimal response. Due to persistent refractory disease, he was referred for consideration of CD19-CAR T-cell therapy. He underwent autologous collection and successful manufacture of a CD19-CAR product, Tisagenlecleucel. Following

bridging therapy with a modified hyper-CVAD regimen and Venetolcax, he developed pancytopenia and did not have hematological recovery prior to admission for CAR T-cell therapy.

He received lymphodepleting (LD) chemotherapy with fludarabine and cyclophosphamide prior to CD19-CAR T-cell infusion. On day +7 post CD19-CAR T-cell infusion, he developed grade 2 CRS requiring one dose of tocilizumab. At time of discharge, on day +13 he remained pancytopenic and transfusion dependent. On day +19, he presented with fever and hypotension in the setting of typhlitis and was admitted to the intensive care unit (ICU). He continued to have severe hypotension and developed a cardiac arrest requiring cardiopulmonary resuscitation with compressions and epinephrine, intubation, and pressor support. Blood cultures were positive for *Clostridium septicum* , and he improved after initiation of antibiotic therapy with meropenem. However, on day +30, he developed another episode of culture negative septic shock again requiring transfer to ICU for pressor support and intubation for tenuous hemodynamic status. CT scan of the abdomen demonstrated an extensive inflammatory process consistent with typhlitis and colitis, with edema of the right rectus muscle and subcutaneous abdominal wall edema. He recovered from this event after re-initiation of broad-spectrum antibacterial therapy but on day +47 again developed septic shock, requiring a third admission to ICU for pressor support. Blood cultures grew *Enterobacter faecium* and *Staphylococcus epidermidis* . An abdominal MRI demonstrated worsening of intrabdominal process, now with a fluid collection tracking in the right para colic gutter extending from the tip of the liver to the level of the cecum, with no discrete wall to suggest abscess, likely due to ongoing pancytopenia. Given ongoing intrabdominal signs and symptoms, multiple episodes of septic shock and pancytopenia, he required continued empiric broad spectrum antibacterial therapy. To evaluate etiology of pancytopenia, he underwent BM evaluations (on day +22 and day +43 post CD19-CAR T-cell infusion) that showed a markedly hypocellular marrow with severely decreased trilineage hematopoiesis, without evidence of recurrent leukemia.

Due to persistent pancytopenia and recurrent life-threatening infections, he received a CD34+ HSCB (5.1 x10^6 CD34+ cells/kg) from his sibling HSCT donor on day +69. Neutrophil recovery occurred on day +13 and platelet engraftment occurred on day + 16 following the CD34+ HSCB. He had no further episodes of septic shock or bacteremia following the CD34+ HSCB. Complete radiological resolution of ongoing intrabdominal process was documented on day + 65 after CD34+ HSCB and empiric antibacterial therapy was discontinued. He did not develop graft-versus- host-disease (GVHD). Importantly, he had continued and ongoing B-cell aplasia (BCA) at 9 months post CD19-CAR T-cell therapy and 6 months following the CD34+ HSCB and remains in complete remission (CR; no detectable disease by flow cytometry or next generation sequence testing) suggesting no interference from the infused donor CD34+ HSCB.

Hematotoxicity is a known side effect of CAR T-cell therapy and can have devastating consequences including risk of hemorrhage and life-threatening infections compounded by concurrent B-cell aplasia, leading to high rates of morbidity and mortality (3). The ELIANA CD19-CAR T-cell trials found 37% of patients had cytopenia that did not resolve by day 28 (1). Juluri et al., highlighted prolonged and persistent cytopenias amongst adult patients with ALL of whom only 85% had neutrophil and 82% platelet recovery at a median follow up of 3 years (4). While LD chemotherapy can play a role, the etiology is likely multifactorial since hematotoxicty has also been observed in patients who did not receive it (5). High grade CRS has been shown to be associated with delayed hematopoietic recovery (3, 4). Other studies show that baseline cytopenias (6) and patients who received prior allogeneic transplants, particularly those who received CAR T-cells less than one year following transplant, were at increased risk (7). Our patient received CD19-CAR T-cell therapy within one year of transplant and had severe baseline cytopenia suggesting he was at higher risk for hematotoxicity, despite the absence of high-grade CRS. The CAR-HEMATOTOX score helps predict hematotoxicity in adult patients with lymphoma who receive CD19 CAR T cell therapy and has been shown to be a useful tool that has been validated in multiple cohorts (6). However, a similar model needs to be validated for patients with ALL.

While eventual recovery from hematotoxicity may be possible, patients are at high risk of succumbing to infections (8). CD34+ HSCB can be a useful therapeutic intervention to shorten the duration of pancytopenia. It can be either autologous (auto) or derived, from the recent transplant donor (allogeneic; allo).

The successful use of autoCD34+ HSCB following CAR T-cell therapy induced hematotoxicity has been reported in case reports and recently in a larger retrospective study of 31 patients (9). The majority (84%) of patients responded and time to response corelated with duration of preceding neutropenia. However, 4/5 patients with active infection did not respond and all non-responders died. For patients with ALL, autoCD34+HSCB is not an option due to BM involvement. While alloCD34+ HSCB is commonly used in the post-transplant setting to rescue hematopoiesis (10), there is limited data regarding its use following CAR T-cell therapy. Recently, two small case series have highlighted the successful use of alloCD34+HSCB (11, 12). Rapid hematopoietic recovery was noted following alloCD34+ HSCB without evidence of GVHD and one patient developed CRS following the boost, presumably due to CD19+ B cells in the product.

In conclusion, we highlight the safety and efficacy of an alloCD34+ HSCB in our patient with severe hematotoxicity and life-threatening infections following CD19-CAR T-cell therapy. The alloCD34+ HSCB had no apparent effect on the activity of CD19-CAR T cells since the patient continued to have B-cell aplasia and remains in CR. Thus, patients with ALL who receive CD19-CAR T-cell therapy after HSCT and develop hematotoxicity might benefit from earlier use of alloCD34+ HSCB to reduce the risk of hemorrhage and life-threatening infections. Larger studies are needed to that assess its safety, efficacy, and optimal timing post CAR T-cell therapy.

Author contributions

Contribution: A.L. and S.N. conceived and prepared the manuscript. Y.L and B.T. provided administrative and regulatory support; A.L, L.B., E.H., S.G., G.M., B.T. and S.N evaluated and cared for the patient; A.L., Y.L and S.N. analyzed and interpreted the data; A.L. and S.N. wrote the manuscript; and all authors approved the final draft of the manuscript and are accountable for all aspects of the work.

Conflict-of-interest disclosure

B.T. received travel support from Miltenyi. S.G. is a co-inventor on patent applications in the fields of cell or gene therapy for cancer. He is a consultant of TESSA Therapeutics, a member of the Data and Safety Monitoring Board (DSMB) of Immatics, and has received honoraria from Tidal, Catamaran Bio, Sanofi, and Novartis within the last 2 years. All other authors have no conflict of interest to disclose.

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