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ARTICLE

Autologous stem cell boost improves persistent immune effector cell associated hematotoxicity following BCMA directed chimeric antigen receptor T (CAR T) cell therapy in multiple myeloma

Meera Mohan [1]✉, Aniko Szabo [2], Anannya Patwari[1], Jean Esselmann[1], Tanvi Patel[3], Ramya Bachu[3], Lisa E. Rein[3], Abhishek Janardan[4], Vineel Bhatlapenumarthi[1], Evanka Annyapu[4], Catherine Skoog[1], Areyl Goff[1], Samer Al Hadidi [3], Sabarinath Venniyil Radhakrishnan[1], Sharmilan Thanendrarajan[3], Maurizio Zangari[3], Nirav Shah [1], Frits van Rhee [3], Binod Dhakal[1], Mehdi Hamadani [1], Anita D'Souza [1] and Carolina Schinke [3]

Persistent Immune Effector Cell Associated Hematotoxicity (ICAHT) is a significant side effect of BCMA CAR T-Cell therapy in patients with relapsed multiple myeloma (MM). The use of stem cell boosts in ICAHT has been described, however studies have been limited by small patient numbers and short follow up. Herein, we report on our multi-institutional experience of ICAHT, defined by an absolute neutrophil count (ANC) of ≤ 1000, thrombocytopenia with a platelet count ≤ 50,000 or/and anemia as hemoglobin (hgb) ≤9 g/dL, in patients who received BCMA CAR T therapy, and the effects of subsequent stem cell boost on hematopoietic reconstitution and clinical outcome. In this study, ICAHT was observed in 60% ($n = 61/101$) of patients at D + 21, and risk factors for its development included history of a prior ASCT, higher number of prior lines of therapy, a decreased platelet count prior to lymphodepletion and history of ICANS. 28% of patients with ICAHT received a stem cell boost at a median of 116 days due to profound and prolonged cytopenias often requiring ongoing transfusion support. Stem cell boost significantly improved cytopenias at 3 and 6 months follow up without any adverse effects on PFS and OS, underscoring the safety of this procedure.

INTRODUCTION

Immune Effector Cell Associated Hematotoxicity (ICAHT) encompasses unique hematological toxicities following novel immune therapies such as chimeric antigen receptor T (CAR T) cell therapy and bispecific antibodies [1–9]. The resulting, sometimes profound, and prolonged cytopenias, are associated with increased morbidity, such as high rates of infections and bleeding and may limit the options for further anti-MM therapy once the patient relapses post CAR T cell therapy. ICAHT has serious clinical consequences which include the exacerbating B cell aplasia with associated hypogammaglobinemia, increased susceptibility to infections both contributing to higher morbidity and mortality [10].

Cytopenias are indeed the most common adverse effect seen followed CAR T cell therapy. Early cytopenia can be attributed to factors such underlying disease burden, extensive prior chemotherapy including stem cell transplantation, bridging chemotherapy, lymphodepletion regimens, type and variations in peak, expansion, and persistence of various CAR T constructs [11]. In addition, acute toxicities associated with CAR T cell therapy such as cytokine release syndrome (CRS), hemophagocytic

lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) can contribute to ICAHT [12–16].

While the pathophysiology of ICAHT remains diverse, emerging evidence indicates that pre-existing disruptions of bone marrow microenvironment and inflammatory states could be contributory [17]. In the context of CD-19 CAR T, 3 distinct patterns of ICAHT have been described [11, 13]. The majority of patients experience intermittent drops in the blood counts about a month after CAR T infusion following initial recovery of counts. Additionally, some patients can have a quick recovery of counts after CAR T infusion after the initial drop, while other may experience an aplastic trajectory with prolonged and profound cytopenias. Furthermore, studies have shown that cytokine profiling of patients with ICAHT revealed elevations of the serum levels of IFN-γ, IL-6 and IL-8, which exhibit patterns similar to those observed in acquired bone marrow failure states such as acquired aplastic anemia and hypocellular myelodysplastic syndrome [18, 19]. Management of patients who experience an aplastic-like ICAHT course is challenging with poor responses to growth factors and thrombopoietin (TPO) agonist [11, 20].

[1]Division of Hematology/Oncology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA. [2]Division of Biostatistics, Institute of Health and Equity, Medical College of Wisconsin, Milwaukee, WI, USA. [3]Myeloma Center, University of Arkansas for Medical Science, Little Rock, AR, USA. [4]Medical College of Wisconsin Medical School, Milwaukee, WI, USA. ✉email: memohan@mcw.edu

In recent pivotal clinical trials and real-world studies of patients undergoing B-cell maturation antigen (BCMA) CAR T cell therapy for multiple myeloma (MM), a significant percentage have exhibited persistent ICAHT [2, 4–6, 21]. Severe and prolonged cytopenia has several implications in clinical practice such as increased susceptibility to infections, needs for prophylactic antibiotics, need for growth factor support, transfusion requirement, poor quality of life, financial toxicity and further complicate anti-MM therapy once the patient relapses post CAR T cell therapy. While growth factor support is widely applied in patients with ICAHT, the effects are usually short lived. Consequently, the use of stem cell boost in ICAHT as a more permanent solution has been described, however studies have been limited by small patient numbers and short follow up [10, 22]. Herein, we report on our multi-institutional experience of ICAHT in patients who received autologous BCMA CAR T cell therapy for MM both in commercial and clinical trial settings.

METHODS
Patient population and ICAHT definition
This study included 108 patients with relapsed refractory MM who received BCMA CAR T cell therapy either on a clinical trial or as standard of care (idecabtagene vicleucel [ide-cel] or ciltacabtagene autoleucel [cilta-cel]) at 2 academic centers in the US, Medical College of Wisconsin, Milwaukee, WI, and University of Arkansas for Medical Sciences, Little Rock, AR. Data including patient demographics, disease characteristics (including bone marrow biopsy), fluorescence in situ hybridization (FISH) studies, novel imaging positron emission tomography–computed tomography [PET-CT] at the most recent assessment before starting lymphodepletion chemotherapy (LD) were collected. High risk disease was defined as the presence of translocations t(4;14); t(14;16); t(14;20); 1q21 copy number abnormalities, deletion (17p) by FISH or presence of ≥ 3 PET-CT defined focal lesion [23]. Cytokine release syndrome (CRS) and Immune effector cell associated neurotoxicity syndrome (ICANS) were graded according to the American Society for Transplantation and Cellular Therapy consensus [24]. Management of CRS and ICANS were done according to institutional guidelines.

The following definitions were used in this study, neutropenia is absolute neutrophil counts of ≤ 1000 cells/μL, thrombocytopenia is platelet count of ≤ 50 × 10^9/L, anemia is hemoglobin ≤ 9 g/dl. ICAHT was defined as the presence of any one of these, neutropenia, thrombocytopenia, or anemia. Neutropenia was characterized by absolute neutrophil counts of ≤ 1000 cells/μL, and thrombocytopenia was defined as a platelet count of ≤ 50 × 10^9/L based on grade 3 CTCAE. Anemia, indicated by a hemoglobin level ≤9 g/dl, was derived from CAR T HEMATOX, a validated scoring system predicting ICAHT in CAR T therapy recipients [25]. Count recovery is defined as absolute neutrophil counts of > 1000 cells/μL, platelet count of >50 × 10^9/L and hemoglobin is >9 g/dl. Data of blood counts were collected on 21 days (D + 21), 3 months, and 6 months post CAR T cell infusion. We chose D + 21 as the timeline of interest as most patients in our practices are closely monitored for about 3 weeks post CAR T-cell infusion with daily labs. Subsequently follow up and labs are modified based on patient's clinical status. Management of ICAHT including use of prophylactic anti-microbials, use of granulocyte-colony stimulating factors (G-CSF), TPO agonist. The decision for application of stem cell boost was at the discretion of the treating physician per institutional guidelines.

Statistical methods
Potential risk factors for cytopenia and ICAHT status at D + 21, 3- and 6-month post CAR T cell infusion using a Fisher's exact test for each categorical variable and a Wilcoxon rank-sum test for each continuous or ordered variable. Overall survival (OS) and progression-free survival (PFS) estimates were calculated using Kaplan-Meier methods. OS and PFS were also modeled by Cox Proportional Hazards regression landmarked from CAR T cell infusion. All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, http://www.R-project.org). All tests were two-sided and $p < 0.05$ was considered statistically significant. All analyses employed an "available case" approach to missing data.

The study was approved by the Institutional Review Board of the coordinating institution (Medical College of Wisconsin) and subsequently by all participating institutions. The research was performed in compliance with the terms of the declaration of Helsinki. Data cutoff was July 31st, 2023.

Table 1. Patient characteristics.

Characteristic	$N = 108$
Median Age (IQR)	64 (57, 69)
Female	43 (40%)
Race	
Caucasians	95 (88%)
African American	12 (11%)
Asian	1 (1%)
Heavy chain subtype, n (column %) *	
IgA	27 (27%)
IgG	73 (73%)
Light chain subtype, n (column %)	
Kappa	73 (68%)
Lambda	34 (32%)
High risk FISH or PET features, n (column %)	64 (59%)
Type of CAR T cell product	
Investigational CAR T	52 (48%)
Ide-cel	42 (39%)
Cilta-cel	14 (13%)
Number of prior ASCT, n (column %)	
0	11 (10%)
1	58 (54%)
2	25 (23%)
3	13 (12%)
4	1 (0.9%)
Median prior lines of therapy at CAR T cell therapy listing (IQR)	5 (4, 6)
Median absolute neutrophil count at CAR T cell therapy listing (IQR)	2.65 (1.75, 3.64)
Median platelet count at CAR T cell therapy listing (IQR)	167 (105, 209)
Use of systemic steroids, n (column %)	27 (25%)
Use of tocilizumab, n (column %)	66 (62%)
CRS (grade), n (column %) [a]	
0	19 (19%)
1	50 (50%)
2	31 (31%)
3	1 (1.0%)
ICANS (grade), n (column %) ¡	
0	80 (86%)
1	4 (4.3%)
2	2 (2.2%)
3	3 (3.2%)
4	4 (4.3%)

IQR: Interquartile range; *Missing data in 8 patients.
[a]Missing data in 7 patients; ¡ Missing data in 15 patients

RESULTS
108 patients were included in this analysis and their baseline characteristics are shown in Table 1. The median age of this cohort was 64 (57–69) years with 40% ($n = 43/108$) being females. About 11% of the patients were African American. The most common MM immunoglobulin subtype was IgG ($n = 73/108$; 73%). About 59% ($n = 64/108$) patients were high risk either by FISH (defined by the presence of translocations t(4;14); t(14;16); t(14;20), 1q21 copy number abnormalities and/or deletion 17p) or PET-CT (≥ 3
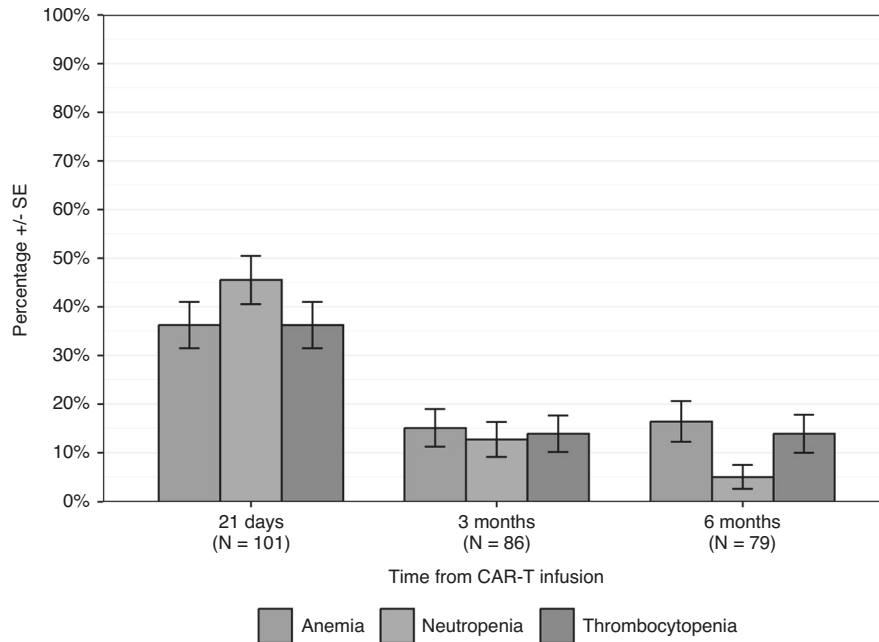
Fig. 1 Box plot. Proportion of patients with anemia, neutropenia, and thrombocytopenia at 21 days, 3 months, and 6 months after BCMA CAR T cell infusion.

avid focal lesions). The majority of patients ($n = 97/108$; 90%) had received at least one autologous stem cell transplant (ASCT) and 39/108 patients (36%) have had ≥ 2ASCTs. The median prior lines of therapy at the time of CAR T cell therapy were 5 (1–12). The median neutrophil and platelet count prior to LD and CAR T therapy was 2.65 (0.6–8.34) cells/µL and 167 (24–488) x 10^9/L, respectively. 42/108 (39%) of patients received ide-cel and 14/108 (13%) cilta-cel while the rest of the patients (52/108) were treated with BCMA directed investigational CAR T cell therapy (clinical trial).

At D + 21 post CAR T cell infusion, 101/108 (94%) of patients were evaluable for the occurrence of ICAHT. 46/101 (46%) of patients had neutropenia and about 36% of patients had thrombocytopenia (37/101) and/or anemia (37/101) each (Fig. 1). The presence of any cytopenia or ICAHT was seen in 60% ($n = 61/101$) of patients at D + 21 post CAR T (Fig. 2). The median ANC for patients with ICAHT at D + 21 was lower at 0.72 (0.17–1.04) cells/µL compared to those who did not develop ICAHT (ANC = 1.98 cells/µL, range 1.04–5.2, $P = <0.001$); similarly median platelet count (43 × 10^9/L vs. 102 × 10^9/L, $p = <0.001$) and hemoglobin (8.9 g/dL vs. 11.4 g/dL, $p = 0.001$) were significantly lower in patients with ICAHT compared to those without.

Risk factors that were associated with the development of ICAHT at D + 21 post CAR T cell infusion emphasize that the extent of prior therapy significantly increased the occurrence of ICAHT. A higher number of prior ASCTs (≥2) and more prior median lines of therapy were significantly associated with ICAHT, $p < 0.001$. Patients with ICAHT had furthermore a lower baseline platelet count (146 × 10^9/L vs. 194 × 10^9/L, $p = 0.005$) compared to those without ICAHT. The presence of ICANS (0% vs. 19%; $p = 0.012$) and the use of tocilizumab (45% vs. 72%; $p = 0.012$) were also more common with patients who experienced ICAHT at D + 21 post CAR T infusion, however the occurrence of CRS was not significantly different (83% vs. 81%; $p = 0.390$). There was also no significant association with the development of ICAHTs when taking into account the different BCMA CAR T cell products.

We furthermore analyzed the use of a stem cell boost on count recovery and outcome in patients with ICAHT. The majority of patients (97%; $n = 59/61$) who had ICAHT at D + 21 had stem cells
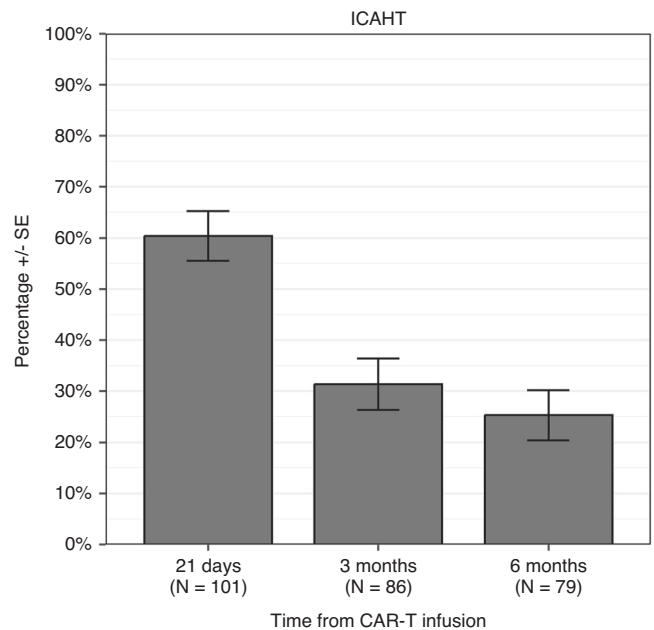

Fig. 2 Box plot. Proportion of patients with ICAHT at 21 days, 3 months, and 6 months after BCMA CAR T cell infusion.

in storage underscoring that the availability of such was not a limiting factor in the present study. A total of 16/59 (28%) patients with ICAHT received a stem cell boost at a median of 116 (29–270) days from CAR T infusion and the median dose of stem cell infused was 3.84 (1.05–9.04) x 10^6 cells/kg. ICAHT patients who received a stem cell infusion had significant higher grades of cytopenias at D + 21 compared to ICAHT patients who did not receive stem cell support, evident by a lower platelet count (24 × 10^9/L vs. 48 × 10^9/L, $p = 0.002$) and hgb (8.45 g/dL vs. 9 g/dL, $p = 0.001$). Median ANC also tended to be lower in patients who received a stem cell boost, albeit not significantly (0.41 cells/µL vs. 0.8 cells/µL, $p = 0.18$). At 3 and 6 months there was a significant

Table 2. Complete blood counts for ICAHT patients pre and post CD34 boost at 3 and 6 months.

3 Months	Pre boost ($n = 14$)	3 months post boost ($n = 14$)	*p*-value
Median ANC cells/μL (range)	0.72 (0–2.6)	3.05 (0.82–8.00)	<0.001
Median Plt count x10^9/L (range)	29.5 (8–53)	127 (14–265)	0.001
Median Hgb g/dL (range)	8.8 (4.3–10.5)	11.0 (7.7–14)	<0.001
6 Months	**Pre boost ($n = 9$)**	**6 months post boost ($n = 9$)**	***p*-value**
Median ANC cells/μL (range)	0.73 (0.44–2.5)	3.1 (2.1–7.52)	0.008
Median Plt count x 10^9/L (range)	32 (8–38)	151 (18–343)	0.008
Median Hgb g/dL (range)	8.7 (4.3–10.2)	10.5 (7.8–13.0)	0.014

Paired tests comparing levels between pre and post boosts at 3 and 6 months, among boosted patient with data for both timepoints.

increase of cell counts in patients who received a boost, as shown in Table 2. At 3 months, the median ANC rose from 0.72 cells/μL to 3.1 cells/μL at ($p = 0.001$), median platelet count from 29.5×10^9/L to 127×10^9/L ($p = <0.001$) and median hgb from 8.8 to 11 g/dL($p = <0.001$) in patients who received a stem cell boost with a similar pattern at 6 months, emphasizing that count recovery post stem boost is prompt and durable. Of note is that ICAHT patients who did not receive a stem cell boost also had some degree of count recovery, albeit with lesser increment than those who received a stem cell infusion, Table 3. Yet, it appears that patients with ICAHT, regardless of whether they received stem cell support, did not achieve the same level of blood count recovery compared to non ICAHT patients. Particularly the platelet count ($p = 0.057$) and hgb ($p = <0.001$) remained substantially lower in ICAHT patients compared to their non ICAHT counterparts, Table 3.

In a next step we analyzed whether the occurrence of ICAHT and/or the administration of a stem cell boost had any influence on clinical outcome. With a median follow up time of 10.6 months the 12-month PFS and OS of the whole patient cohort were 59.9% (95% CI: 50.6–70.8%) and 78.9% (95% CI: 70.9–87.8%) respectively (supplement Fig. 1). Adjusted Cox proportional hazards regression analysis was performed factoring in variable such as patient's age, high risk FISH features, EMD, prior lines of therapies, type of CAR T cell product and ICAHT. After adjusting for potential contributing factors, only the presence of high-risk FISH features (HR = 1.91, 95%CI: 1.05–3.48; $p = 0.035$) was associated with inferior PFS, emphasizing that the infusions of stem cells post CAR T cell therapy has no adverse impact on disease progression. For OS, the number of prior lines of therapy (HR = 1.2, 95% CI 1.0–1.44, $p = 0.05$) and occurrence of ICAHT at D + 21 (HR = 3.41, 95% CI 1.07–10.9; $p = 0.038$) adversely impacted outcome. The infusion of a stem cell boost was not able to mitigate the ICAHT associated inferior OS (HR = 2.54, 95% CI 0.91–6.96, $p = 0.071$), albeit the follow up was possibly too short to accurately investigate the long-term impact. Lastly, we investigated whether the occurrence of secondary AML/MDS was associated with ICAHT, however these events were rare and developed in only 2 patients, one who had no ICAHT and the other one who had ICAHT without stem cell boost.

DISCUSSION

ICAHT is one of the most prevalent toxicities seen following CAR T cell therapy. In our series, about 60% of patients had ICAHT 3 weeks after CAR T cell infusion. Neutropenia, a significant cytopenia with substantial clinical consequence was present nearly 50% of patients in the initial 3 weeks after CAR T cell infusion. In our study, recipient of prior ASCT and higher number of prior lines of therapy were associated with higher incidence of ICAHT. A lower baseline bone marrow reserve and lower platelet counts were also more common in patients with ICAHT [21]. As previously shown, CAR T cell therapy associated toxicity such as

ICANS and use of tocilizumab was also more common in patients with ICAHT suggesting that the high degree of inflammation seen in ICANS, or higher-grade CRS might contribute to the delay in recovery of hematopoietic progenitor cells [16]. Interestingly, the occurrence of any grade CRS was not associated with ICAHT as likely CRS occurs in nearly all MM patients treated with CAR T cell therapy. Tocilizumab which binds irreversibly to IL6 receptor has been shown to inhibit IL-6 mediated signaling through these receptors [26]. IL-6 has been implicated in thrombocytosis and tocilizumab use could potentially impede thrombopoiesis by disrupting IL-6 signaling [27].

In our series, 28% of patients with ICAHT received a stem cell boost at a median of 3 months post CAR T cell infusion. The application of stem cell infusion was higher than in previous reports likely due to widespread availability of preserved stem cell grafts (~97%) [10, 21, 22]. Stem cell infusions resulted in 100% neutrophil engraftment with a minority of patients still having persistent anemia and thrombocytopenia at 6 months despite the statistically and clinically significant improvement in these absolute levels of hemoglobin and platelet.

Multiple studies have so far shown that ICAHT in MM patients treated with BCMA CAR T cell therapy affects the majority of patients. In the registrational studies of autologous BCMA CAR T therapy, cytopenias were observed in majority of patient in the first 30 days following CAR T infusion [4, 28]. While cytopenias and ICAHT can improve over time, there is a significant body of literature showing that these adverse effects can also persist beyond 3–6 months. Real world data has shown that ≥ grade 3 hematological toxicities were present in 75% of patients treated with commercial ide-cel or cilta-cel during the first 100 days post CAR T infusion [25]. In another real-world experience of ide-cel ($n = 52$), 40% of patients had persistent ≥ grade 3 cytopenia at D + 90 with 28% patients remaining thrombocytopenic and 11% neutropenic [21]. Thus overall, these studies highlight the significant clinical burden of ICAHT in MM patients treated with BCMA CAR T cell therapy resulting in increased morbidity, risk of infections and worse clinical outcome. Here, we show that the occurrence of ICAHT at D + 21 is further associated with worse OS. Interestingly, the infusion of stem cells and subsequent count recovery did not appear to mitigate the adverse impact of ICAHT on OS. One reason for this might be the high number of previous therapy lines in patients with ICAHT, suggesting that there are only limited treatment options post CAR-T disease relapse. This however will likely change in the near future with the expanding therapeutic landscape of relapsed MM, particularly the use of bispecific antibody therapy. Given that there will be more treatment options available for patients with CAR T cell failure, an adequate count recovery will be crucial to continue further treatment. Alternatively, the limited duration of follow up in the present study did not allow for a clear understanding of the actual impact of subsequently therapies for post CAR T cell therapy relapses.

Table 3. Blood Counts by groups based on D + 21 ICAHT and boost status at 6 month.

Timepoint	Characteristic	No ICAHT at D + 21 (n = 40)	ICAHT at D + 21, no stem cells (n = 49)	ICAHT at D + 21, + stem cells (n = 12) [a]	p-value
D + 21	Median ANC cells/µL (range)	1.98 (1.0–5.2)	0.82 (0–2.99)	0.41 (0.1–3.2)	<0.001
	Median Plt count x10^9/L (range)	102 (84–144)	48 (15–220)	24 (11–119)	<0.001
	Median Hgb g/dL (range)	11.3 (10.7–11.9)	9 (7.1–13.5)	8.445 (6.7–9.2)	<0.001
3 months	Median ANC cells/µL (range)	2.36 (2.0–4.2)	1.7 (0.3–9.37)	3 (0.02–6.79)	0.012
	Median Plt count x10^9/L (range)	157 (115–195)	108 (20–244)	107 (7–273)	0.009
	Median Hgb g/dL (range)	11.8 (10.75–13.45)	10.2 (7.1–13.7)	9.45 (7.1–12.5)	<0.001
6 months	Median ANC cells/µL (range)	2.87 (0.66–5.8)	2.48 (0.3–7.4)	3.1 (1.18–4.46)	0.432
	Median Plt count x10^9/L (range)	148 (122–197)	89 (50–190)	115 (83–168)	0.057
	Median Hgb g/dL (range)	12.6 (8–15.40)	10.8 (9.75–11.90)	10 (8.6–11.5)	<0.001

ANC absolute neutrophil count, PLT platelet, Hgb hemoglobin
[a] A total of 16 patients received a stem cell boost, however for this analysis we only included 12 patients who a stem cell boost and had data points at the 3 times lines D + 21-, 3- and 6-months post CAR T infusion.

Previous studies have already focused on identifying patients at risk of ICAHT. The CAR-HEMATOTOX score emerged as an easy to use, risk stratification tool based on clinical variable (including cell counts, C-reactive protein and ferritin) present prior to starting lymphodepleting chemotherapy that is predictive of ICAHT [13]. This was developed in the context of CD19 CAR T therapy and later validated in an independent cohort of MM patients treated with BCMA CAR T therapy [25]. In a multi-institutional study of MM patients treated with commercial BCMA CAR T about 44% of patients had a high CAR-HEMATOTOX score, and this was associated with higher rates of clinically significant cytopenia, prolonged severe neutropenia, severe infections and higher 1-year non-relapse mortality mostly related attributed to infections [25]. In this study, a higher CAR-HEMATOTOX score was independently associated with inferior PFS and OS [25]. More recently, in an effort to harmonize the definition and management of ICAHT, the European Hematology Association (EHA) and European Society of Blood and Marrow Transplantation (EBMT) put forth expert recommendations. In this report, an early stem cell boosts as early as D + 14 after CAR T cell infusion is recommended in patients with severe neutropenia refractory to G-CSF support.

The utilization of stem cell boosts for ICAHT varies between 8 to 19% across various series and this is likely largely influenced by institutional practices and the availability of stored stem cell in storage for MM patients [21, 22]. Moving forward, we believe that it will be essential for patients with high risk of ICAHT to have stem cells in store prior to CAR T cell therapy. This scenario will likely be even more important in the future with the potential use of sequential CAR T cell therapy, once different products targeting different antigens will become readily available. These observations also emphasize the need for adequate upfront stem cell collection in MM patients. Currently, fludarabine, the standard LD chemotherapeutic agent used prior to CAR T therapy is well known to be bone marrow toxic including the risk of development of MDS. Alternative lymphodepleting regimens such as single agent bendamustine or cyclophosphamide may deserve further exploration as CAR T therapy become more widely adopted and will be employed in earlier lines of therapy [29].

Our study has several limitations inherent to the retrospective design. About 50% of patients in this study received an investigational CAR T product in early phase ½ studies potentially impacting the observed clinical outcomes. There was no clearly defined threshold or timeline for stem cell boost, and this was largely at the physician's discretion. Additionally, we are limited by the relatively smaller sample size and shorter follow up. Further studies are needed to understand the optimal cell count threshold, timing, and dose of stem cell boosts, as well as to explore healthcare resource utilization in the setting of ICAHT.

In conclusion, our manuscript underscores the significant and complex challenges associated with ICAHT in the setting of BCMA CAR T cell therapy for MM. A significant proportion of patients had early ICAHT with persistence beyond the initial period adding to significant morbidity and mortality. Stem cell boost for ICAHT is safe and effective in management of ICAHT. It is crucial to establish clear guidelines for upfront stem cell collection and preservation of stem cell graft, particularly in the context of clinical trials exploring upfront CAR T cell therapy challenging ASCT in newly diagnosed MM, as well as the anticipated reduced utilization of salvage ASCT due to numerous available therapy options in the relapsed setting. Future research will need to focus on development of strategies to mitigate ICAHT associated with BCMA CAR T cell therapy to optimize patient outcome.

DATA AVAILABILITY
Data will be provided upon reasonable to the corresponding author.

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Conception and design: MM MD, MS; CS MD. Provision of study materials or patients: MM MD, MS; JE RN; CS PA; AG APRN; SAH MD MS; SVR MD; ST MD; MZ MD; NS MD; FvR MD Ph.D.; BD MD, MS; MH MD; AD'S MD, MS; CS MD. Collection and assembly of data: MM MD, MS; JE RN; TPq, MD; RB MD; AJ BA; VB MD; EA BS; CS MD. Data analysis and interpretation: AS Ph. D, LER Sc, MM MD, MS; CS MD. Manuscript writing: MM MD, MS; CS MD. Final approval of manuscript: All author. Non-Author Contributions to Data Collection, Analysis, Or Writing/Editing Assistance: Not Applicable.

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Correspondence and requests for materials should be addressed to Meera Mohan.

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