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CANCER THERAPY AND PREVENTION

Filgrastim associations with CAR T-cell therapy

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Abstract

Little is known about the benefits and risks of myeloid growth factor administration after chimeric antigen receptor (CAR) T-cell therapy for diffuse large B-cell lymphoma (DLBCL). We present a retrospective analysis among 22 relapsed/refractory DLBCL patients who received CAR T-cell therapy with axicabtagene ciloleucel. Filgrastim was administered by physician discretion to seven patients (31.8%), and the median duration of neutropenia after lymphodepleting therapy was significantly shorter for those patients who received filgrastim (5 vs 15 days, P = .016). Five patients (22.7%) developed infection in the 30 days post-CAR T-cell therapy with three patients being Grade 3 or higher. There was no difference in the incidence and severity of infection based on filgrastim use (P = .274, P = .138). Among the seven patients that received filgrastim, six patients (85.7%) and four patients (57.1%) had evidence of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), respectively. Among the 15 patients that did not receive filgrastim, 8 patients (53.3%) and 7 patients (46.7%) had evidence of CRS and ICANS, respectively. There was no significant difference in the incidence of developing CRS or ICANS between the group of patients that received filgrastim and those that did not (P = .193, P = .647). However, there was a significant increase in the severity of CRS for patients that received filgrastim compared to those that did not (P = .042). Filgrastim administration after CAR T-cell therapy may lead to an increase in severity of CRS without decreasing infection rates.

KEYWORDS

chimeric antigen receptor T-cell therapy, cytokine release syndrome, diffuse large B-cell lymphoma, filgrastim, immune effector cell-associated neurotoxicity syndrome

1 | INTRODUCTION

While chimeric antigen receptor (CAR) T-cell therapy is an exciting advancement in the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), its application is limited by associated toxicities, including cytokine release syndrome (CRS), neurotoxicity and severe cytopenias, with 78% of patients developing Grade 3 or higher neutropenia in the ZUMA-1 trial.[1] Recombinant granulocyte colony-stimulating factor (G-CSF) has been widely used to shorten the duration of neutropenia and risk of infection in other settings, such as neutropenic complications after conditioning for hematopoietic cell transplant.[2] However, in CAR T-cell therapy, myeloid growth factors have the potential to increase the incidence and/or severity of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) by promotion of proinflammatory cytokine

Abbreviations: ANC, absolute neutrophil count; ASTCT, American Society of Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN, interferon; IL, interleukin; IQR, interquartile range; RICE, rituximab/ifosfamide/carboplatin/etoposide.

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secretion from monocytes and macrophages.[3-5] Preclinically, monocytes and macrophages are the main source of interleukin (IL)-1 and IL-6 during CRS.[4,5] Surprisingly, CRS severity is mediated not by CAR T-cell-derived cytokines, but by those of monocytes and macrophages.[4,5] Therefore, we sought to determine if a relationship exists between filgrastim administration, which stimulates myelopoiesis and enhances granulocyte function, and CRS. There is currently a lack of evidence to guide clinicians on the benefits and risks of recombinant myeloid growth factor use in CAR T-cell treatment.

TABLE 1 Baseline patient and disease characteristics

	All patients (N = 22)
Age at time of CAR T-cell therapy (median, IQR)	65.0 (57.0, 68.8)
≥65	12 (54.6%)
<65	10 (45.5%)
Gender	
Male	12 (54.6%)
Female	10 (45.5%)
Ethnicity	
Caucasian	12 (54.6%)
Hispanic	7 (31.8%)
Asian	0 (0%)
African American	1 (4.6%)
Other	2 (9.1%)
Disease type	
DLBCL NOS	5 (22.7%)
Transformed follicular	2 (9.1%)
Richter's transformation	1 (4.6%)
High-grade DLBCL	14 (63.6%)
Cell of origin	
GCB	10 (45.5%)
Non-GCB	10 (45.5%)
Unspecified	2 (9.1%)
Relapse or Refractory	
Relapse	15 (68.2%)
Refractory	7 (31.8%)
Number of prior therapies	
<3	9 (40.9%)
≥3	13 (59.1%)
ASCT prior to CAR T-cell therapy	1 (4.6%)
ECOG at time of CAR T-cell therapy	
0-1	21 (95.5%)
2-4	1 (4.6%)
Bridging therapy given before CAR T-cell therapy	
Yes	10 (45.5%)
No	12 (54.6%)

Abbreviations: ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; NOS, not otherwise specified.

What's new

Chimeric antigen receptor (CAR) T-cell therapy in patients with relapsed/refractory diffuse large B-cell lymphoma is limited by associated cytokine release syndrome, neurotoxicity, and cytopenias. Little is known about the benefits and risks of myeloid growth factor administration in CAR T-cell therapy. This retrospective analysis reveals a significant increase in the severity but not the incidence of cytokine release syndrome in those patients that received filgrastim. There was no association of filgrastim use with the severity or incidence of neurotoxicity and infection rates. The findings call for caution in the use of myeloid growth factors in patients undergoing CAR T-cell therapy.

2 | MATERIALS AND METHODS

Between March 2018 and May 2019, we reviewed 22 patients with DLBCL treated with axicabtagene ciloleucel with or without concurrent use of filgrastim. Prior to CAR T-cell infusion, all patients received standard lymphodepleting therapy with fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day on days −5 through −3, except for one patient that received reduced doses for chronic kidney disease Stage IV (fludarabine 15 mg/m^2/day and cyclophosphamide 375 mg/m^2/day). Prophylactic tocilizumab 8 mg/kg was given to all patients at 36 hours after CAR T-cell infusion, with additional doses of tocilizumab and/or steroids given for evidence of CRS/ICANS based on the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system.[6] Filgrastim was administered at physician discretion after CAR T-cell infusion at a weight-based dose of either 300 or 480 mcg, and cumulative filgrastim dose was recorded within the first 30 days. Toxicity after CAR T-cell therapy was also assessed up to 30 days postinfusion. Any patient with neutropenic fever was treated with broad-spectrum antibiotics; no prophylactic antibiotics were given. Documented infections were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[7] Antibiotics were also administered for any confirmed infections. Chi-squared test or Cochran-Armitage test were performed to examine association between cohort characteristics and the study variable of administration with or without filgrastim.

3 | RESULTS

Baseline patient characteristics are displayed in Table 1. The median age at the time of CAR T-cell therapy was 65.0 years (interquartile

range [IQR], 57.0-68.8). The majority (14 patients, 63.6%) had high-grade DLBCL, while 5 patients had DLBCL not otherwise specified, 2 patients had transformed follicular lymphoma and 1 patient had Richter's transformation. Seven patients (31.8%) had refractory DLBCL, while 15 patients (68.2%) had relapsed DLBCL with a median number of relapses prior to CAR T-cell therapy of 1.0 (IQR, 0.0-2.0). Thirteen patients (59.1%) had received greater than or equal to three prior therapies. Only one patient (4.6%) had received autologous hematopoietic cell transplant prior to CAR T-cell therapy. Ten patients (45.5%) received bridging therapy for high disease burden before CAR T-cell therapy, which included rituximab/gemcitabine-oxaliplatin (7 patients), cytarabine/thiotepa (1 patient), rituximab/dexamethasone/cytarabine/cisplatin (1 patient), rituximab/ifosfamide/carboplatin/etoposide (RICE, 1 patient) and rituximab/cyclophosphamide/dexamethasone (1 patient). The number of cycles of bridging therapy ranged from 1 to 3 with a median of 2.

Seven of the 22 patients (31.8%) received filgrastim by physician discretion at a target dose of 5 mcg/kg/day with 3 patients receiving 300 mcg/day and 4 patients receiving 480 mcg/day. The median start day of filgrastim was 2 days post-CAR T-cell therapy (range Day −2 to Day +7), and the median number of filgrastim doses was 6 (range, 3-18). The median duration of neutropenia after CAR T-cell therapy was 5 days (IQR, 4.5-8.5) for patients who received filgrastim compared to 15 days (IQR, 8.0-30.0) for patients who did not receive filgrastim (P = .016; Table 2). Fourteen patients (63.6%) developed neutropenic fever after CAR T-cell therapy, 6 of whom received filgrastim and 8 of whom had not (P = .193; Table 2). Five patients (22.7%) developed an infection in the 30 days post-CAR T-cell therapy including *Clostridium difficile* colitis (one patient, Grade 3), *Enterococcus faecalis* bacteremia (one patient, Grade 4), pneumonia (one patient, Grade 3) and Herpes simplex virus (two patients, Grades 1 and 2). Among the seven patients that received filgrastim, three patients (42.9%) developed an infection and two patients (28.6%) developed a Grade 3 or greater infection. Among the 15 patients that did not receive filgrastim, 2 patients (13.2%) developed an infection and 1 patient (6.7%) developed a Grade 3 or greater infection. There was no difference in the incidence and severity of infection between patients who received filgrastim and those that did not (P = .274, P = .138; Table 2; Figure 1).

CRS was noted in 14 patients overall (63.6%), and 4 patients (18.2%) had Grade 3 or higher CRS. Among the seven patients that received filgrastim, six patients (85.7%) had evidence of CRS and three patients (42.9%) had Grade 3 or higher CRS. Among the 15 patients that did not receive filgrastim, 8 patients (53.3%) had evidence of CRS and 1 patient (6.7%) had evidence of Grade 3 or higher CRS. ICANS was noted in 11 patients overall (50.0%), and 9 patients (40.9%) had Grade 3 or higher ICANS. Among the seven patients that received filgrastim, four patients (57.1%) had evidence of ICANS and three patients (42.9%) had evidence of Grade 3 or higher ICANS. Among the 15 patients that did not receive filgrastim, 7 patients (46.7%) had evidence of ICANS and 6 patients (40.0%) had Grade 3 or higher ICANS. There was no significant difference in the incidence of developing CRS (any grade) or ICANS (any grade) between the group of

TABLE 2 CAR T-cell associated toxicity

	All patients (N = 22)	G-CSF administered (N = 7)	G-CSF not administered (N = 15)	*P* value
Median duration of neutropenia (days) (IQR)	10 (6.0, 25.8)	5 (4.5, 8.5)	15 (8.0, 30.0)	.016
Febrile neutropenia				
No	8 (36.4%)	1 (14.3%)	7 (46.7%)	.193
Yes	14 (63.6%)	6 (85.7%)	8 (53.5%)	
New infection				.274
None	17 (77.3%)	4 (57.1%)	13 (86.7%)	
Any grade	5 (22.7%)	3 (42.9%)	2 (13.2%)	
CRS				.193
None	8 (36.4%)	1 (14.3%)	7 (46.7%)	
Any grade	14 (63.6%)	6 (85.7%)	8 (53.3%)	
ICANS				.647
None	11 (50.0%)	3 (42.9%)	8 (53.3%)	
Any grade	11 (50.0%)	4 (57.1%)	7 (46.7%)	
Steroids given				.648
No	9 (40.9%)	2 (28.6%)	7 (46.7%)	
Yes	13 (59.1%)	5 (71.4%)	8 (53.3%)	
More than one dose of tocilizumab given				.074
No	10 (45.5%)	1 (14.3%)	9 (60.0%)	
Yes	12 (54.6%)	6 (85.7%)	6 (40.0%)	

Abbreviations: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; G-CSF, granulocyte colony-stimulating factor; ICANS, immune effector cell-associated neurotoxicity syndrome.

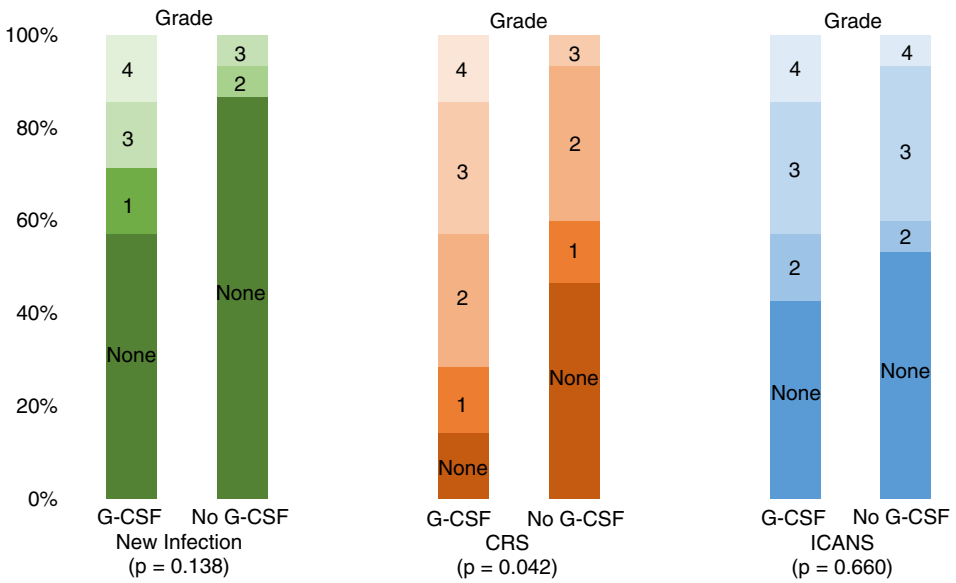

FIGURE 1 Severity of chimeric antigen receptor (CAR) T-cell associated toxicities based on granulocyte colony-stimulating factor (G-CSF) use. ICANS, immune effector cell-associated neurotoxicity syndrome [Color figure can be viewed at wileyonlinelibrary.com]

patients that received filgrastim and those that did not (P = .193, P = .647; Table 2). There was, however, a significant increase in the severity of CRS for patients that received filgrastim compared to those that did not (P = .042), but no increase in the severity of ICANS based on filgrastim use (P = .660; Figure 1).

Thirteen patients (59.1%) received corticosteroids after CAR T-cell treatment at a median cumulative dosage of 666.7 mg prednisone equivalents (IQR, 445.0-933.3), with the majority (9 patients, 69.2%) receiving steroids in the first 5 days post-CAR T-cell infusion. Half of the patient cohort (12 patients, 54.6%) required at least one dose of tocilizumab in addition to the scheduled prophylactic dose. Among the seven patients that received filgrastim, 5 patients (71.4%) received corticosteroids and 6 patients (85.7%) received more than one dose of tocilizumab. Among the 15 patients that did not receive filgrastim, 8 patients (53.3%) received corticosteroids and 6 patients (40.0%) received more than one dose of tocilizumab. There was no association between filgrastim use and steroid use or administration of additional doses of tocilizumab (P = .648, P = .074).

4 | DISCUSSION

At our institution, filgrastim was administered after CAR T-cell therapy at physician discretion with less than half of our patient cohort receiving filgrastim (seven patients, 31.8%). Importantly, although the median duration of neutropenia was significantly lower for patients who received filgrastim, there was no difference in the development or severity of infections (P = .274, P = .138). Instead, while patients given filgrastim were not more likely to develop CRS (P = .193), the severity of CRS was higher in those that received filgrastim (P = .042), as has been suggested by preclinical data modeling myeloid growth factors in combination with CAR T-cells.[4,5] The development of CRS is related to activation of in vivo T-cell expansion and the production of T-cell effector cytokines, including IL-6, IL-10 and interferon (IFN)-γ,[8] which are also downstream products of myeloid cells stimulated by filgrastim. One preclinical study showed that higher levels of murine G-CSF correlated strongly with CRS severity and survival.[5] Elevated systemic levels of IL-6 in particular have been associated with severe CRS, and IL-6 receptor blockade with the monoclonal antibody tocilizumab is an important agent used to reduce CRS toxicity.[9,10] Of all the cytokines analyzed in the ZUMA-2 study, only peak levels of granzyme B and granulocyte-macrophage colony stimulating factor (GM-CSF, a closely related protein to G-CSF) were associated with severe CRS and severe ICANS.[11]

CAR T-cell associated neurotoxicity has been associated with elevations in similar inflammatory markers to CRS (IL-6, IL-10, IFNγ), in addition to higher serum levels of G-CSF and GM-CSF.[12,13] Mouse models of CRS and ICANS have suggested that the main driver of CAR T-cell neurotoxicity is actually IL-1 secretion from activated macrophages.[4,5] Unlike its efficacy in CRS, tocilizumab did not protect mice from lethal neurotoxicity, a finding analogous in humans; however the IL-1 receptor antagonist anakinra abolished both CRS and neurotoxicity.[4,12] Interestingly, in addition to its stimulatory effects on granulocytes, filgrastim has immunomodulatory effects on other immune cells and can inhibit inflammatory cytokine production within monocytes or macrophages.[14] This may account for why we found no association with filgrastim and the development or severity of neurotoxicity (P = .647, P = .660). GM-CSF, which induces both granulocytes and macrophages, may be more closely tied to neurotoxic effects and, in fact, GM-CSF inhibition has been shown to reduce neuroinflammation and prevent CRS.[15]

The guidelines on use of filgrastim and other growth factors with CAR T-cell therapy are not standardized. While some recommend administration of myeloid growth factors once absolute neutrophil count (ANC) decreases to <500/μL and to continue until ANC increases to ≥1500/μL,[16] others recommend administration of filgrastim only if patients develop Grade 1 CRS at the same time as neutropenia or in the setting of neutropenic fever.[17] The use of myeloid

growth factors across institutions employing CAR T-cell therapy is also mixed. In an electronic survey on the current administrative, logistic and toxicity management practices of CAR T-cell therapy across the United States by the ASTCT, out of 28 respondents, 46% used growth factor if allowed by product labeling, 29% never administered growth factor, 14% determined the use of growth factor on a patient-specific basis and 11% administered growth factor to all patients.[18]

Although our study is limited by its small sample size and retrospective nature, we suggest that myeloid growth factor administration be used with caution in patients undergoing CAR T-cell therapy. We found an association between filgrastim use and CRS severity, suggesting that increasing the number of patients in the study would strengthen the association. However, the effect size of the association was small. Further studies are required to determine the safety of myeloid growth factors after CAR T-cell therapy.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

ETHICS STATEMENT

This study was approved by the University of California Los Angeles Institutional Review Board. Informed consent was not required for this study.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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