Growth Factor in the Setting of CAR T-Cell Therapy: To Use or Not to Use

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Abstract

Patients undergoing chimeric antigen receptor (CAR) T-cell therapy may experience side effects including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), neutropenia, and infection. Growth factor has historically been used to treat neutropenia; however, its role in CAR T-cell therapy is not well explained. Existing data on the safety and efficacy of growth factor are conflicting. The purpose of this integrative review was to explore the safety and efficacy of growth factor in adult patients with hematologic malignancies undergoing CAR T-cell therapy. A literature review was conducted using PubMed, Cumulative Index to Nursing & Allied Health (CINAHL), and Scopus databases. A total of 2,635 articles were retrieved. Four studies were included that looked at the use of growth factor in the CAR T-cell setting. Safety outcomes evaluated included CRS, ICANS, neutropenic fever and/or infection, and neutropenia duration. Efficacy outcomes evaluated included CAR T-cell expansion and treatment response. The literature suggests that growth factor may not increase CRS prevalence, but may lead to an increased grade of CRS, namely grade 2. Growth factor administration does not have any association with ICANS toxicity, CAR T-cell expansion, or treatment response. Its use may not necessarily lead to decreased infection rates but may shorten the duration of neutropenia. Practice implications for providers working with this unique patient population include using growth factor early in the course of CAR T-cell therapy as treatment to shorten the duration of neutropenia rather than infection prophylaxis.

Chimeric antigen receptor (CAR) T-cell therapy is a treatment modality in which patients' T lymphocytes are harvested, reengineered, and reinfused to display a receptor that later recognizes and helps to destroy malignant cells. CAR T-cell therapy was first approved in 2017 and revolutionized treatment approaches for patients with relapsed or refractory lymphoma, acute lymphocytic leukemia, multiple myeloma (MM), and even some

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solid tumor malignancies (Baird et al., 2021; National Cancer Institute, 2022). Since then, several CAR T-cell products have come to market. Each product varies according to its costimulatory domain, treatment indications, and side-effect profile. Generally, however, side effects are similar across all products and include cytokine release syndrome (CRS), cytopenias, infection, and immune effector cell–associated neurotoxicity syndrome (ICANS; Adkins, 2019; Baird et al., 2021).

Although CAR T-cell therapy has delivered promising results changing the landscape of treatment of hematologic malignancies, it also comes with unique risks (Adkins, 2019; Hansen et al., 2021). Neutropenia is one expected major side effect (Bupha-Intr et al., 2020). Growth factor, which includes granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), has long been used for febrile neutropenia prophylaxis (Gawade et al., 2020). Growth factors are proteins that stimulate new blood cell production. Their function is multifaceted. They help maintain the viability of progenitor cells, block apoptosis, promote cell division and phagocytosis, and influence the maturation of progenitor cells (Link, 2022). However, the role of growth factor in CAR T-cell therapy remains controversial due to the theoretical risk of CRS exacerbation (Hansen et al., 2021).

Cytokine release syndrome is a heightened inflammatory response triggered by CAR T cells that bind to cancerous cells leading to their destruction (Adkins, 2019). This destruction leads to vascular endothelial damage and a cascade of cytokine release such as interferon-γ, GM-CSF, interleukin (IL)-10, and IL-6, and other immune effector cells (Hernani et al., 2022). Cytokine release syndrome affects 42% to 93% of CD19 CAR T-cell therapy patients (Hernani et al., 2022). Symptoms usually present within the first week of CAR T-cell therapy administration and as late as 3 weeks after infusion (Adkins, 2019). Cytokine release syndrome may also cause biphasic, triphasic, or recurrent cytopenias with the first occurrence within 3 to 4 weeks after infusion (Sharma et al., 2022). Low-grade CRS management includes supportive care with fluid resuscitation and symptom management. Meanwhile, those with high-grade CRS may require corticosteroids and/or an anti–IL-6 receptor antagonist such as tocilizumab (Actemra), which can exacerbate neutropenia (Si & Teachey, 2020).

Although several CRS grading criteria exist, including the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, Lee criteria, Penn criteria, Memorial Sloan Kettering Cancer Center (MSKCC) criteria, and CAR T-Cell Therapy–Associated Toxicity (CARTOX), consensus grading established by the American Society for Transplantation and Cellular Therapy (ASTCT) were published in 2018 in efforts to streamline identification and treatment (Lee et al., 2019). Grading criteria vary based on clinical symptoms and treatment recommendations by stage. At least two doses of tocilizumab must be available at any given time at certified hospitals per the Risk Evaluation and Mitigation Strategy (REMS) program for CAR T-cell approved therapies. Patients must also stay within 2 hours of a certified administering hospital for at least 4 weeks following CAR T-cell infusion (Kite Pharma Inc., 2022).

Pharmacokinetically, growth factor such as GM-CSF works by stimulating monocyte production and further differentiation into granulocytes, including neutrophils, monocytes, macrophages, and dendritic cells (Bo et al., 2011). Landmark trials such as ZUMA-1, which examined CD19 CAR T cells in diffuse large B-cell lymphoma (DLBCL), have referenced elevated GM-CSF levels and corresponding CRS (Sterner et al., 2019). There is, therefore, understandable concern over using growth factor to manage neutropenia in patients receiving CAR T-cell therapy. Since most patients will develop neutropenia, there is an urgent and ongoing need to further understand the processes by which CRS occur and to clarify whether growth factor is a safe and effective treatment option for patients receiving CAR T-cell therapy. There is little published literature on the relationship between growth factor and CRS.

The pathophysiology of ICANS remains unknown, although its incidence may vary from 23% to 67% in patients with lymphoma and 40% to 62% in patients with leukemia (Hansen et al., 2021; Santomasso et al., 2019). Theories include the passive seepage of cytokines through the blood-brain barrier and T-cell transport into the central nervous system (Neelapu et al., 2017). Symptoms are reversible and may include aphasia, seizures,

obtundation, confusion, and encephalopathy (Adkins, 2019; Hansen et al., 2021). The median onset after CAR T-cell therapy is 4 to 6 days with a median duration of 14 to 17 days (Adkins, 2019). Little literature exists evaluating the relationship between growth factor and ICANS.

Ambiguity regarding growth factor use is exacerbated by conflicting publications. Some product package inserts specifically recommend against using growth factor while others make no reference to growth factor (Adkins, 2019). Furthermore, National Comprehensive Cancer Network (NCCN) guidelines advise growth factor to be considered as needed, leaving the decision to physician discretion. Treatment guidelines may also vary by institution based on national guidelines.

The purpose of this integrative review is to present and synthesize the findings of studies reporting the safety and efficacy of growth factor in patients undergoing CAR T-cell therapy. Considerations around growth factor use, its implications, and opportunities for future research are also discussed.

METHODS

A medical librarian was consulted and helped perform a literature search of PubMed, Cumulative Index to Nursing & Allied Health (CINAHL), and Scopus databases. The search was performed using key terms to identify articles pertaining to growth factor, CAR T-cell therapy, and CRS. Medical subject heading terms included "granulocyte colony stimulating factor," "chimeric antigen," "T-cell," "GM-CSF" OR "GCSF" OR "granulocyte-macrophage" OR "granulocyte," and "cytokine release" OR "CRS." Inclusion criteria specified English-language publications between 2017 (the inception of CAR T-cell therapy) and December 14, 2022, and studies that looked at growth factor administration and measured CRS in adult patients undergoing CAR T-cell therapy for any hematologic malignancy. Exclusion criteria included studies not pertaining to growth factor, those focusing on animal studies, and CAR T-cell treatment in solid malignancies. A total of 2,635 articles were retrieved. After removing duplicates (n = 579), 680 were selected for title and abstract screening, resulting in additional exclusions (n = 666). Full-text screening was completed on 14 articles, with 10 excluded as they did not look at growth factor specifically as an intervention in CAR T-cell therapy or were informational overviews of CAR T-cell therapy. One in-text reference was reviewed but ultimately excluded as it was a commentary. A total of four studies that met all inclusion and exclusion criteria were included in this review (Figure 1) and are summarized in Table 1.

RESULTS

The results are organized by safety and efficacy outcomes. Safety outcomes include CRS and ICANS incidence and severity, neutropenic fever and infection, and duration of neutropenia. Efficacy outcomes include CAR T-cell expansion and treatment response. Table 2 summarizes the published studies looking at growth factor utilization in patients undergoing CAR T-cell treatment.

All studies were cohort studies observing the effect of growth factor administration at different time points along the CAR T-cell continuum in a population of mostly lymphoma patients. Participant sample sizes ranged from 9 to 244. Although the studies varied according to when growth factor was administered, they all addressed two areas that served as the framework for this review: observed safety and/or efficacy outcomes.

Safety: CRS Incidence and Severity

All four studies discussed CRS incidence and severity (Gaut et al., 2020; Jiang et al., 2022; Liévin et al., 2022; Miller et al., 2022).

Gaut and colleagues (2020) evaluated a cohort of 22 relapsed/refractory (R/R) DLBCL patients, seven of whom received G-CSF (filgrastim) following CAR T-cell administration and 15 who did not. The authors reported no significant difference in the CRS incidence, with six cases in the G-CSF group and eight in the no G-CSF group. However, the CRS in the G-CSF group was more likely to be more severe, or higher grade, compared with the no G-CSF group (p = .042).

In contrast, Miller and colleagues (2022) retrospectively investigated the impact of G-CSF on 197 patients with lymphoma and 47 patients with MM in Massachusetts who received CAR T-cell therapy. Within the lymphoma cohort, the intervention group (71%, n = 140) consisted of those patients who received prophylactic G-CSF before CAR T-cell infusion. The control group was stratified into those

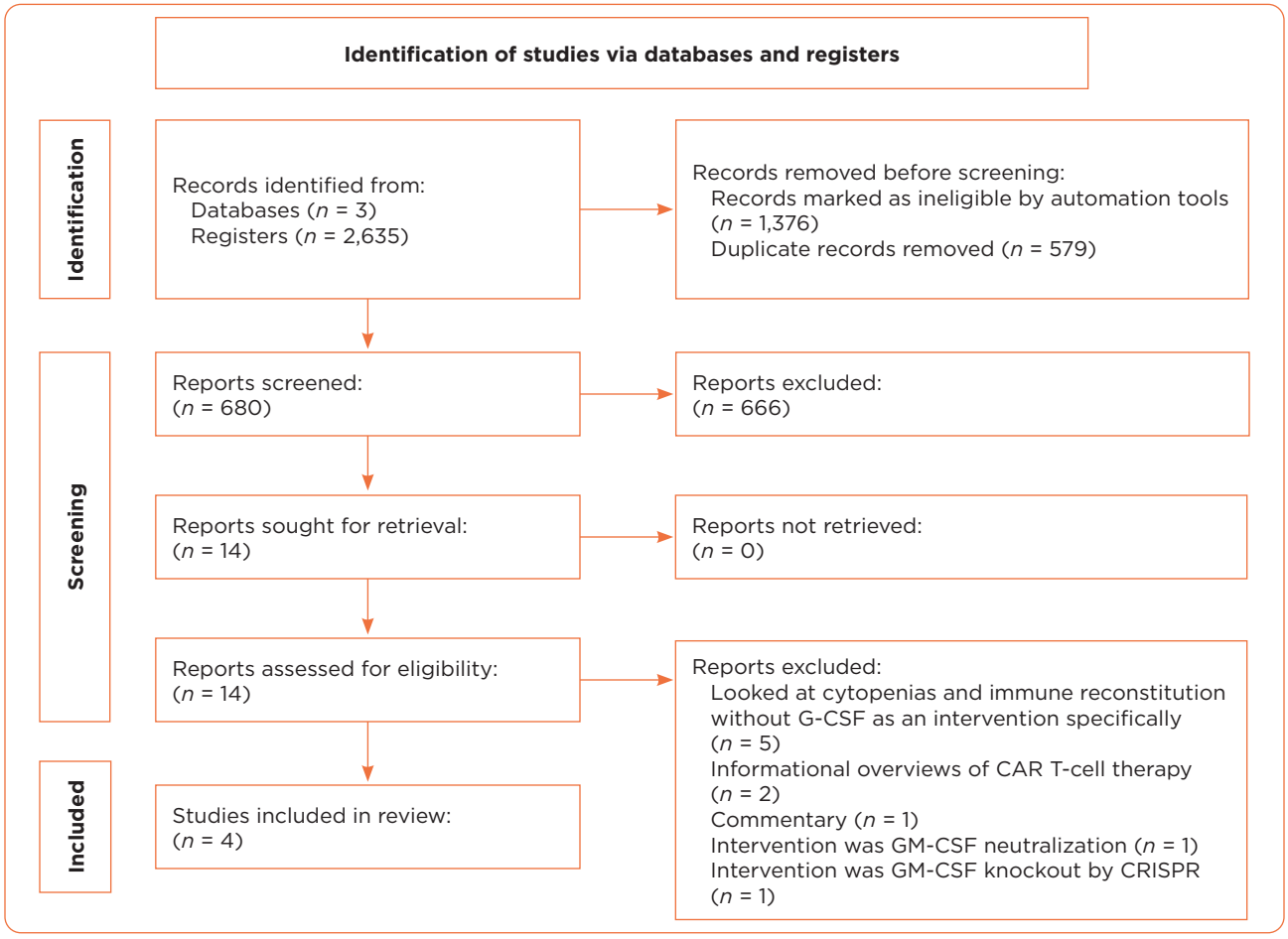

Figure 1. PRISMA flow diagram.

who did not receive G-CSF (31.9%, $n = 15$) or received G-CSF following CAR T-cell infusion (89.3%, $n = 42$). Grade ≥ 2 CRS occurred more often in the intervention group than in the overall control group (52% vs. 19%, $p < .01$). Within the control group, 13% of those who did not receive G-CSF developed grade ≥ 2 CRS compared with 21% of those who received it after CAR T-cell therapy, but the difference was not significant. This finding is in contrast to the retrospective analysis of the 22 lymphoma patients observed by Gaut and colleagues (2020) who also received G-CSF after CAR T-cell infusion yet showed statistically significant differences in severity of CRS among patients who received G-CSF compared with those who did not.

Miller and colleagues (2022) observed similar CRS toxicity rates in their cohort of 47 MM patients who were stratified based on early (intervention group) and later (control group) G-CSF administration. Within the early (≤ 2 days after CAR T-cell infusion) G-CSF group of 24 patients, 12 (50%) patients developed grade 1 CRS, 8 (33.3%) developed grade 2 CRS, and no patients developed grade ≥ 3 CRS. In the control group, 21 (91.3%) patients received later (≥ 3 days) G-CSF and 2 patients (8.7%) did not receive G-CSF. Overall, 23 (48.9%) developed grade 1 CRS, 16 (34.0%) developed grade 2 CRS, and 1 (2.1%) developed grade 3 CRS. However, it was not reported whether the patients who did not receive G-CSF developed CRS. The incidence of developing any-grade CRS appeared to be similar whether patients did or did not receive G-CSF after CAR T-cell infusion.

In a retrospective review by Liévin and colleagues (2022), 122 R/R lymphoma patients in France received either early G-CSF (at day 2 post–CAR T-cell infusion), no G-CSF, or late G-CSF (5 days post–CAR T-cell infusion). The late and no administration groups served as the control. Similar rates of overall and grade 3 to 4 CRS toxicity were reported for both the administration and control groups. There were

Table 1. Results Summary

	Safety				Efficacy	
Study	**CRS**	**ICANS**	**Febrile neutropenia and infection**	**Neutropenia duration**	**CAR T-cell expansion**	**Treatment response**
Gaut et al. (2020)	No significant difference in CRS incidence; significant increase in severity of CRS in patients that received GCSF	No association	No significant difference in incidence and severity between GCSF and no G-CSF groups	No significant difference between G-CSF and no G-CSF groups	NA	NA
Jiang et al. (2022)	No CRS reported	No ICANS reported	Infection in 2 of 9 patients Did not report on febrile neutropenia	Significantly higher neutrophil count between baseline and third week after administration (p = .037)	7 of 9 patients experienced CAR T-cell expansion in peripheral blood during GM-CSF usage	66% overall response rate ORR 50% OS at 365 days following CAR T-cell infusion
Liévin et al. (2022)	No significant difference in any-grade CRS between early and late G-CSF groups	No significant difference in any-grade ICANS between early and late G-CSF groups	Significantly decreased incidence of febrile neutropenia (p = .018) in early G-CSF group	Similar duration of grade 4 neutropenia between early G-CSF and control group	No difference in quality of CAR T-cell expansion between early G-CSF and control group	No significant difference in ORR, OS, or PFS between early and late G-CSF group
Miller et al. (2022)	Lymphoma cohort: Frequency of grade ≥ 2 CRS higher in prophylactic G-CSF group (p < .01) but comparable rates of grade ≥ 3 CRS between prophylactic and control groups Within control group, no difference in CRS rates between those who received G-CSF and those who did not MM cohort: No significant difference in CRS toxicity	Lymphoma cohort: Prophylactic G-CSF not associated with ICANS MM cohort: No significant difference in ICANS toxicity	Lymphoma cohort: No difference in IV antibiotic use for neutropenic fever between prophylactic and control group MM cohort: No significant difference between control and experimental group in developing severe neutropenia	Lymphoma cohort: Time to ANC recovery (> 0.5 × 10^9/L) faster in the prophylactic group (3 vs. 4 days, p < .01) MM cohort: G-CSF group had significantly shorter duration of neutropenia compared with control group, with median of 6 vs. 10 days (p < .01)	NA	CR rates similar between prophylactic and control groups for both lymphoma and MM groups

Note. ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; ICANS = immune effector cell–associated neurotoxicity syndrome; NA = not addressed; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Table 2. Studies Showing Growth Factor Use in CAR T-Cell Therapy

Author	Study design	Sample	Intervention	Findings	Limitations
Gaut et al. (2020)	Cohort study Level of evidence: IV	Population: DLBCL (DLBCL NOS, transformed follicular, Richter transformation, high-grade DLBCL) *N* = 22 Median age: 65.0 Country of origin: USA	Filgrastim administered at 300 µg or 480 µg daily per physician discretion to 22 lymphoma patients undergoing CAR T-cell therapy	CRS noted in 14 patients overall (63.6%); 4 patients with grade 3 or higher CRS (18.2%). Of 7 patients who received G-CSF, 6 patients (85.7%) had CRS and 3 patients (42.9%) had grade 3 or higher CRS. 14 (63.6%) patients developed neutropenic fever, 6 of whom received filgrastim and 8 who did not. No significant difference in incidence of developing CRS (any grade) between patients who did and those who did not receive G-CSF; however, significant increase in severity of CRS for patients who received G-CSF compared with those who did not. No association between G-CSF use and incidence of any-grade ICANS, neutropenic fever, infection, steroid use, or additional doses of tocilizumab.	No randomization Retrospective study Small sample size
Jiang et al. (2022)	Cohort study Level of evidence: IV	Population: 4 ALL and NHL (several subtypes including DLBCL, Burkitt lymphoma, primary CNS lymphoma, primary mediastinal B cell lymphoma) *N* = 9 Median age: 39 Country of origin: China	GM-CSF (molgramostim) administered to nine patients undergoing CAR T-cell therapy starting at lowest daily dosage of 100 µg/day	No CRS or ICANS reported. No significant increase in inflammatory markers observed. 7 patients (77.8%) experienced CAR T-cell expansion in peripheral blood during GM-CSF usage. Statistically significant difference in neutrophil count between baseline and third week after administration. 4 patients with fever after GM-CSF administration, 2 of which were attributed to infection (pneumonia and UTI).	Study methods and timeline unclear Observational study, unclear whether prospective or retrospective Small sample size

Note. ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CNS = central nervous system; CRS = cytokine release syndrome; 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; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; UTI = urinary tract infection.

no significant differences across any of the groups in the prevalence of any-grade (88 [72.2%] patients) or grade ≥ 2 CRS (37 [30.3%] patients).

Jiang and colleagues (2022), in an observational study of nine patients with acute lymphoblastic leukemia and non-Hodgkin lymphoma in China, reported no association of CRS with GM-CSF (molgramostim) administration after CAR T-cell infusion. Administration of GM-CSF started as early as 8 days up to 126 days following CAR T-cell infusion. Although no CRS was reported, inflammatory markers associated with CRS were measured before and after initial GM-CSF administration. These markers included CRP, IL-17F, IL-1β, IL-4, TNFα, and TNF-β, all of which demonstrated significant decreases 4 weeks after exposure ($p < .05$).

Table 2. Studies Showing Growth Factor Use in CAR T-Cell Therapy (cont.)

Author	Study design	Sample	Intervention	Findings	Limitations
Miller et al. (2022)	Cohort study Level of evidence: IV	Population: Lymphoma and MM *N* = 197 (Lymphoma) *N* = 47 (MM) Country of origin: USA	G-CSF administered to two different cohorts: lymphoma and MM patients. Within the lymphoma population, G-CSF was administered after CAR T-cell infusion or not at all (control group) or prophylactically with mostly pegylated G-CSF prior to CAR T-cell infusion (intervention group). 140 in intervention group and 57 in control group. Within the MM group, G-CSF given ≥ 3 days (control group) or early (≤ 2 days, intervention group) after CAR T-cell infusion. 24 in intervention group (early G-CSF administration) and 23 in control group.	Lymphoma cohort: In lymphoma patients, 84 (43%) experienced grade ≥ 2 CRS, with 11 patients (6%) having grade ≥ 3 CRS. Frequency of grade ≥ 2 CRS higher in prophylactic G-CSF group (52% vs. 19%, $p < .01$). Grade ≥ 3 CRS comparable (6% vs. 4%, $p = .52$) between prophylactic group and control group. Within control group, no significant toxicities between those who received G-CSF after CAR T-cell therapy (*N* = 42) and G-CSF non-exposed patients (*N* = 15) for grade ≥ 2 CRS (21% vs. 15%, $p = .71$). 151 (77%) developed severe neutropenia (ANC < 0.5) within a median of 3 days after CAR T-cell infusion. Time to ANC recovery (> 0.5) was faster in the prophylactic group (median of 3 vs. 4 days, $p < .01$). No difference in proportion of infections or ICANS between prophylactic and control groups. Complete response (CR) rates similar between prophylactic and control groups. MM cohort: Grade > 2 CRS occurred in 17 (36%) of patients, 1 case of grade 3 CRS (4.3%). No significant difference in toxicities, including incidence of severe neutropenia and time to develop CRS or treatment response. Early G-CSF group had significantly shorter duration of neutropenia compared with control group, with median of 6 vs. 10 days ($p < .01$).	No randomization Retrospective study Lack of multivariate analyses to address baseline differences between cohorts

Note. ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CNS = central nervous system; CRS = cytokine release syndrome; 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; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; UTI = urinary tract infection.

Safety: ICANS

All four studies discussed ICANS incidence and severity (Gaut et al., 2020; Jiang et al., 2022; Liévin et al., 2022; Miller et al., 2022).

In their small retrospective study of 22 R/R lymphoma patients, Gaut and colleagues (2020) reported no significant difference in the development of ICANS in 17 patients who received G-CSF compared with the seven who did not. Furthermore, receiving G-CSF did not predispose patients to developing a lesser or more severe grade of ICANS.

In the larger study of 197 lymphoma patients in Massachusetts, Miller and colleagues (2022) also reported similar levels of ICANS toxicity between patients who received G-CSF (pegfilgrastim) prophylactically and after CAR T-cell infusion. The

Table 2. Studies Showing Growth Factor Use in CAR T-Cell Therapy (cont.)

Author	Study design	Sample	Intervention	Findings	Limitations
Liévin et al. (2022)	Cohort study Level of evidence: IV	Population: Relapsed/refractory DLBCL *N* = 122 Country of origin: France	G-CSF was administered to lymphoma patients undergoing CAR T-cell therapy. The control group consisted of patients who did not receive G-CSF or received it later (after day 5). The intervention group included patients who received G-CSF early (starting day 2 post-infusion). 33 in intervention (early G-CSF) group and 89 in control group (34 did not receive any G-CSF, 55 received late G-CSF).	Patients who received early G-CSF experienced similar duration of grade 4 neutropenia but significantly decreased incidence of febrile neutropenia (58% vs. 81%, p = .018) No difference was observed in quality of CAR T-cell expansion. CRS prevalence was not significant between early G-CSF and control group. Any-grade CRS occurred in 88 (72%) of patients. Grade ≥ 2 CRS occurred in 37 (30.3%) patients. No significance in any-grade ICANS or response rate (OS and PFS).	No randomization Retrospective study

Note. ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CNS = central nervous system; CRS = cytokine release syndrome; 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; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; OS = overall survival; PFS = progression-free survival; UTI = urinary tract infection.

development of grade ≥ 2 ICANS in both groups was comparable, with 52 (37%) occurrence in the prophylactic group vs. 17 (30%) in the control group (p = not significant [NS]). In addition, there were no significant differences in ICANS toxicity within the control group of lymphoma patients who did not receive G-CSF at all or received G-CSF after CAR T-cell infusion. This was also true within the same study for the sample of 47 MM patients. Eight (17%) of patients developed ICANS, three of which were grade ≥ 3 ICANS. There was no significant difference in time to grade ≥ 1 ICANS between the intervention and control groups.

Similar findings were described in the French study by Liévin and colleagues (2022), with no differences across groups of any-grade ICANS in a population of 122 lymphoma patients who received early (within 2 days post–CAR T-cell infusion) or late (≥ 5 days of CAR T-cell infusion) G-CSF. In their retrospective study, 32 patients developed ICANS (26.2%), with 16 patients (13.1%) developing grade ≥ 2 or higher. The difference in prevalence of any-grade ICANS or grade ≥ 2 ICANS in those who received early vs. late G-CSF was not significant.

A study of nine patients conducted by Jiang and colleagues (2022) in China measured ICANS using NCCN Guidelines. No ICANS was observed.

Safety: Febrile Neutropenia and Infection

In Gaut and colleagues' (2020) retrospective review of 22 R/R lymphoma patients, 14 patients (63.6%) developed neutropenic fever following CAR T-cell infusion: six who received G-CSF (filgrastim) and eight who did not (NS). Five patients (22.7%) developed infection, including *Clostridium difficile* colitis, *Enterococcus faecalis* bacteremia, pneumonia, and herpes simplex virus within 30 days following CAR T-cell infusion. Three of the seven patients who received G-CSF developed an infection while only two of the 15 who did not receive filgrastim developed an infection, but findings were not statistically significant.

Data on febrile neutropenia were also reported by Miller and colleagues (2022). In the study of 197 patients with lymphoma, 95% developed mild

neutropenia defined as an absolute neutrophil count (ANC) < 1.5 × 10^9/L, with 151 (77%) developing severe neutropenia after CAR T-cell infusion (median of 3 days). Of the 197 lymphoma patients, 126 (64%) received intravenous antibiotics mainly for neutropenic fever with no significant difference between the prophylactic G-CSF and control groups (64% vs. 63%, respectively). In a multivariate analysis, prophylactic G-CSF was associated with a decreased odds ratio (OR) of developing severe neutropenia (OR 0.33, 95% CI = 0.10–0.93, p = .05). Infection was documented in 37 patients (19%) within 30 days of CAR T-cell. Of these 37 patients, there was no significant difference in incidence of infections between those who received G-CSF prophylactically and those who did not. Of note, three patients suffered fatal infections within 30 days of CAR T-cell infusion, two in the control group that received G-CSF following CAR T-cell infusion.

In parallel, 36 of 47 (77%) MM patients within the Miller and colleagues (2022) study developed severe neutropenia with no significant difference between the early G-CSF and no G-CSF groups. Thirty-nine (83%) received IV antibiotics. There was a significantly shorter period of IV antibiotic treatment duration in those who received early G-CSF (median 6 vs. 10 days, p < .01).

In contrast, in the Liévin and colleagues (2022) French study of 122 patients with R/R lymphoma, there was a significant difference in the occurrence of neutropenic fever between the early and control groups (p = .018). Neutropenic fever developed in 33 patients (27%) who received early G-CSF (starting 2 days after CAR T-cell therapy) and in 89 patients (72.95%) in the control group that received G-CSF after day 5 or not at all. Thirty-seven (30%) patients acquired infections (three fungal, 18 viral, and 28 bacterial). In these 37 patients, 11 received G-CSF early (11% of the intervention group), and 26 (29.2% of the control group) received G-CSF at day 5 or greater or not at all (p = NS).

Jiang and colleagues (2022) reported infection in two of nine patients (22.22%) of their nine-patient sample. One patient developed pneumonia prior to GM-CSF administration and the other developed urinary tract infection 5 days after GM-CSF administration. No incidence rates on febrile neutropenia were reported in this study.

Safety: Duration of Neutropenia

The duration of severe neutropenia (ANC < 0.5 × 10^9/L) was reported by two studies. Those who received G-CSF either prophylactically or following CAR T-cell infusion experienced shorter periods of neutropenia (Gaut et al., 2020; Miller et al., 2022). Gaut and colleagues (2020) retrospectively analyzed 22 patients who received or did not receive G-CSF following CAR T-cell infusion. The duration of neutropenia was significantly shorter in those who received G-CSF, with a median of 5 days vs. a median of 15 days in those who did not (p = .016).

Furthermore, Miller and colleagues (2022) reported that within their lymphoma cohort, those who received prophylactic G-CSF had a significantly faster time to neutrophil recovery compared with those who received G-CSF after CAR T-cell infusion (3 vs. 4 days, p < .01). In contrast, the French cohort of 122 patients with R/R lymphoma by Liévin and colleagues (2022) reported no significant difference in the incidence (73% vs. 80%) and duration (5 vs. 4 days) of severe neutropenia between patients who received G-CSF in the first 30 days of CAR T-cell administration and those who received it late or not at all.

Jiang and colleagues (2022) reported that in their nine-patient cohort of ALL and lymphoma patients, the median duration to WBC recovery, defined as an ANC between 3,000 and 5,000 cells/mm^3 was 17 (3–53) days in eight patients. The ninth patient's WBC count was consistently greater than 3,000 cells/mm^3 or 3 × 10^9/L. In this study, moderate neutropenia was defined as an ANC of 1,500 cells/mm^3 and was used to determine the cutoff for growth factor administration. This contrasts with Miller and colleagues (2022) and Liévin and colleagues (2022) who used severe neutropenia as 500 cells/mm^3 or 0.5 × 10^9/L to measure response. All nine patients in this study had received GM-CSF at some point after CAR T-cell infusion, with initial administration date ranging from 8 to 126 days.

Efficacy: CAR T-Cell Expansion

Two studies observed CAR T-cell expansion in relation to growth factor administration. Jiang and colleagues (2022) observed notable increases in CAR T-cell count starting on day 7 (median or mean not reported; range 2–11) after G-CSF administration in seven out of nine patients. Median

baseline and peak CAR T-cell counts in peripheral blood were 0.85 × 10^6/L (0–50.9) and 6.06 × 10^6/L (1.43–112.55), respectively. Two patients did not receive peripheral blood CAR T-cell counts.

Liévin and colleagues (2022) reported no differences in CAR T-cell expansion patterns between their sample of 122 lymphoma patients who received early G-CSF and those who did not. Analyses observing expansion patterns among those who received two different growth factor products were conducted separately. There were no significant differences in the median relative C_{max} (% CAR T-cell/CD3+ T cells) and median absolute C_{max} (number of CAR T-cells/μL) between those who received early G-CSF and those who did not.

Efficacy: Treatment Response

Three studies measured treatment response (Jiang et al., 2022; Liévin et al., 2022; Miller et al., 2022). In the Jiang and colleagues (2022) study of nine patients, two died from infection, one died from cancer-related death, and one died from graft-vs.-host disease (GVHD). Overall survival (OS) measured at 365 days after CAR T-cell administration was 44.4% (four of the nine patients), although this article cites OS as 50%. Overall response rate (ORR) was 66.67%.

Miller and colleagues (2022) measured treatment response in 197 lymphoma and 47 MM patients. In the lymphoma cohort, there was an 82% ORR. One hundred thirty-four (68%) of these patients achieved a complete response (CR), 28 (14%) developed a partial response (PR), 30 (15%) had stable disease or disease progression, and 5 (3%) died before a response assessment could be conducted. The CR rates between the prophylactic G-CSF and control groups were similar (67% vs. 60%, p = NS). Similar rates of progression-free survival (PFS) and overall survival (OS) at 2 years were also noted for the prophylactic and control groups (45.1% vs. 41%, p = NS; 65.0% vs. 59.6%, p = NS, respectively). Seven patients later acquired therapy-related myelodysplastic syndrome or acute myeloid leukemia, although these patients had more prior lines of treatment.

Within the MM group of the Miller and colleagues (2022) study, the ORR was 89%. Thirty-two (68%) patients achieved a CR. Complete responses were similar between those who received early G-CSF and late G-CSF (71% vs. 65%, p = NS). Median PFS was 9.9 months and median OS was 23.2 months, although these measures were not stratified by G-CSF treatment group due to a limited number of patients.

Liévin and colleagues (2022) assessed treatment response in 122 lymphoma patients at months 1, 3, 6, 9, and annually. Complete response rates between the early (day 2 after CAR T-cell infusion), G-CSF, and control groups (no G-CSF or day 5 and beyond) were similar at 1 month (37% vs. 33%, p = NS) and 3 months (55% vs. 58%, p = NS). Overall survival and PFS at 3 months were also similar (p = NS).

DISCUSSION

Collective findings from these studies reflect that growth factor used early in the course of CAR T-cell therapy was generally safe with no adverse impact on treatment responses. Variations in timing of administration further demonstrated that whether growth factor was given prior to or after CAR T-cell infusion, CRS incidence rates may be similar between those who receive growth factor and those who do not. In the studies presented where growth factor was given after CAR T-cell infusion, CRS incidence and severity were not worse except in one study by Gaut and colleagues (2020). It is important to highlight, however, that the small sample size within their study limits the external validity of the findings. Overall, the use of growth factor, either before or after CAR T-cell infusion did not necessarily lead to increased frequency of CRS but was associated with higher severity, specifically grade ≥ 2. Therefore, Gaut and colleagues (2021) suggest using G-CSF with caution while Miller and colleagues (2022) suggest using G-CSF following CAR T-cell infusion as a treatment rather than prophylactic modality for neutropenia. In patients who already developed a low-grade CRS, growth factor was not associated with worsening CRS if administered early in the course of treatment after CAR T-cell infusion (Miller et al., 2022). There was no association between growth factor use and the occurrence of ICANS.

Despite the inconsistencies in the data related to the use of growth factor and the development and duration of severe neutropenia, there is evidence that growth factor use does not actually

improve infection rates. Furthermore, in the Miller and colleagues (2022) study, even with a shorter duration of intravenous antibiotic exposure and faster time to neutrophil recovery, a longer length of hospitalization in patients who received prophylactic G-CSF was observed. Although it is unclear why lymphoma patients treated prophylactically with G-CSF had prolonged hospitalization, it may be attributed to the fact that this group had a higher proportion of patients with aggressive lymphomas, such as DLBCL and high-grade B-cell lymphomas, or were treated with more previous lines of therapy and had less marrow reserve.

One area where the data are clearer is regarding G-CSF efficacy. Of the three studies that examined efficacy, the data indicate that growth factor did not adversely affect CAR T-cell expansion and treatment responses. This suggests that although the short-term safety profile of growth factor remains unclear, it does not have unfavorable long-term impacts on clinical response. It appears that those patients who do receive growth factor may still go on to achieve durable responses.

Challenges presented while appraising the studies included variations in types and timing of growth factor use. Three of the four studies used G-CSF while one study used GM-CSF. Of the three studies that used G-CSF, different products and dosing regimens were used. For example, Miller and colleagues (2022) utilized mostly pegylated G-CSF. Gaut and colleagues (2020) and Liévin and colleagues (2022) strictly used G-CSF. Differences in growth factor preference or utilization may be based on availability depending on where studies were conducted. This may have implications as GM-CSF has a much broader effect on proliferation and differentiation of granulocytes, monocytes, and dendritic cells (Bo et al., 2021). There is some thought that use of GM-CSF over G-CSF may induce a stronger CRS response since notable increases in GM-CSF have been linked in the literature and initial studies of CAR T-cell therapy (Sterner et al., 2019).

The timeline in which growth factor use was observed ranged greatly, with G-CSF being given as early as 2 days prior to CAR T-cell infusion and as late as 126 days after. Each study also stratified their control and intervention groups differently. One group administered prophylactic G-CSF prior to CAR T-cell infusion while some defined early G-CSF as within 2 days of CAR T-cell administration or at 2 days of CAR T-cell administration. The control groups were also often defined as those receiving late G-CSF, which was further defined as day 5 or beyond after CAR T-cell therapy, or even further out in some instances—up to day 23 after CAR T-cell therapy.

Additionally, only one of the studies clarified the use of either autologous and/or allogeneic CAR T-cell administration. Allogeneic, or donor-derived, CAR T cells may theoretically induce a stronger inflammatory response, which could affect CRS outcomes. To our knowledge, only Jiang and colleagues' (2022) study distinguished between its eight patients who received autologous CAR T-cell therapy and one patient who received allogeneic CAR T-cell therapy.

The studies reviewed yielded inconclusive and conflicting data, which could be explained by several limitations. These include retrospective study designs, lack of randomization of the patient sample size, small sample sizes, and multiple variations in the type of growth factor use and the timeline in which they were administered. Two studies were performed outside of the United States where practice guidelines may vary, leading to differences in research objectives and clinical management.

IMPLICATIONS

Growth factor may be a feasible and reasonable treatment option for oncology patients undergoing CAR T-cell therapy. Individualized risk-benefit discussions are warranted for each patient, but the data generally favor growth factor being used as treatment to shorten the time to neutrophil recovery and not as prophylaxis for CAR T-cell therapy. It might also be prudent to use G-CSF rather than GM-CSF, since G-CSF has been studied more often than GM-CSF. Although the data did not show trends towards decreasing intensive care unit admissions, overall length of hospital stay, or rate of infection, its use may still be meaningful in certain scenarios such as in decreasing the duration of neutropenia. Growth factor does not appear to increase the incidence of CRS. However, providers should bear in mind that, if indicated, patients who receive growth factor may develop a more severe form of CRS, namely grade 2. Prompt recognition of these symptoms is key as CRS is reversible and

may become life-threatening if not treated early. In these instances, the provider should follow ASTCT guidelines and administer supportive measures, tocilizumab, and/or steroids accordingly. Since CRS may mimic sepsis, infection should be on the differential and full fever workup should be performed while initiating empiric antibiotics.

CONCLUSION

Despite conflicting data, growth factor may be safe and effective in the management of neutropenia in CAR T-cell therapy patients. Growth factor does not affect overall treatment outcomes, and its role in CAR T-cell therapy is worth investigating. It cannot be excluded as a treatment option without further research from more large, well-designed randomized clinical trials. Future research should look at using growth factor as prophylaxis vs. treatment, timing of growth factor administration, and its use in the autologous vs. allogeneic CAR T-cell setting.

Disclosure

The authors have no conflicts of interest to disclose.

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