REVIEW ARTICLE

Immune effector cell-associated hematotoxicity: mechanisms, clinical manifestations, and management strategies

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment landscape for hematologic malignancies. However, it is frequently complicated by immune effector cell-associated hematotoxicity (ICAHT), a potentially life-threatening adverse event encompassing neutropenia, anemia, and thrombocytopenia. These cytopenias elevate the risk of severe infections, transfusion dependence, and prolonged hospital stays, contributing substantially to morbidity and non-relapse mortality. This review delineates the incidence, mechanisms, and risk factors for ICAHT, highlighting the complex interplay between disease burden, a patient's immune status, and features of the CAR T-cell products. Standardized grading systems, based on the depth and duration of neutropenia, have improved the classification of ICAHT and enabled more consistent risk stratification. Current prophylactic and therapeutic strategies, ranging from growth factor administration to hematopoietic stem cell boosts for refractory cases, are discussed, emphasizing tailored approaches to mitigate severe and prolonged hematotoxicity. These management strategies highlight the need for targeted interventions to prevent ICAHT without compromising the efficacy of the CAR T cells. As CAR T-cell therapy broadens to new indications, optimized ICAHT management could enhance patients' outcomes, reduce healthcare utilization, and increase therapy accessibility.

Introduction

Chimeric antigen receptor (CAR) T-cell therapy has transformed the treatment of hematologic malignancies, offering durable remissions to patients with otherwise refractory disease. Since its initial approval for B-cell acute lymphoblastic leukemia (ALL), CAR T-cell therapy has expanded to multiple indications, including large B-cell lymphoma (LBCL), follicular lymphoma, mantle cell lymphoma, and multiple myeloma (MM). Moreover, its application is advancing into earlier lines of treatment, and recent data suggest potential efficacy in non-malignant conditions such as autoimmune disorders.[1]

Despite these promising outcomes, toxicity remains a significant concern, with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) representing the prototypical adverse events.[2] The incidence of these toxicities varies, depending on the CAR T-cell product,[3-6] disease burden,[7] cytokine profile,[8] as well as multiple factors reviewed elsewhere.[2,8] Beyond CRS and ICANS, CAR T-cell therapy is associated with a spectrum of other toxicities, both short- and long-term, including organ toxicity, infections,[9,10] and second primary malignancies.[11,12] Additional adverse effects, such as hypogammaglobulinemia, B-cell aplasia, and cytopenias, further complicate patients' management and long-term outcomes.[2]

Hematotoxicity, also referred to as immune effector cell-associated hematotoxicity (ICAHT),[13] is a prevalent and clinically significant toxicity associated with CAR T-cell therapy. The increased susceptibility to life-threatening infections arises from several interconnected mechanisms. Neutropenia and lymphopenia, common sequelae of CAR T-cell therapy, severely impair the host immune system's ability to combat bacterial, fungal, and viral pathogens.[9,14,15] This

immunosuppressed state is further exacerbated by B-cell aplasia and hypogammaglobulinemia - frequent off-target effects of B-cell-directed CAR T-cell therapies – which compromise humoral immunity by reducing antibody production. Together, these factors establish a profound immunodeficient environment, positioning infections as a leading cause of non-relapse mortality in patients treated with CAR T cells across diverse clinical settings.[10,16] Moreover, the development of transfusion dependency[17] adds to therapy-related morbidity, extends hospital admissions, and imposes a substantial burden on healthcare resources. This review focuses on the hematologic toxicities associated with CAR T-cell therapy. We examine the frequency, pathophysiology, clinical consequences of, and approaches to managing these toxicities. Furthermore, we explore potential strategies to reduce their occurrence and discuss the implications for improving patients' outcomes.

Definitions

As CAR T-cell therapy expands, a broad spectrum of toxicities has emerged, underscoring the need for standardized criteria to grade and report these effects consistently. Evolving criteria are improving the accuracy of toxicity reporting and facilitating more reliable comparisons across studies. In 2019, the American Society for Transplantation and Cellular Therapy (ASTCT) introduced standardized criteria for CRS and ICANS,[18] which have been widely adopted by the clinical community. These criteria have improved the consistency of reporting and allowed for a more precise evaluation of treatment outcomes.[19]

Similarly, definitions of hematologic toxicities, particularly cytopenias, have evolved. Although clinical trials primarily follow the Common Terminology Criteria for Adverse Events (CTCAE) classification (Table 1), this system does not fully capture the unique patterns of cytopenias seen after CAR T-cell therapy and may not correlate with clinical outcomes.[20-22] Real-world studies have also employed inconsistent definitions, and the classification of prolonged and delayed cytopenias remains particularly variable.[23] Moreover, many reports of delayed cytopenias fail to account for competing events such as disease relapse, subsequent treatments, or death, further complicating the interpretation of cytopenia data.

To address the variability in neutropenia following CAR T-cell therapy, the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) developed a consensus grading system for early (days 0-30) and late (after day 30) neutropenia[13] (Table 1). This system categorizes neutropenia by both depth and duration and has been validated across multiple cohorts, contributing to a more standardized approach for managing hematologic toxicities following CAR T-cell therapy. To facilitate the implementation of this grading system, Liang *et al*. published a computational framework in R that automates the classification of early and late ICAHT grading based on serial absolute neutrophil counts.[24]

Incidence and patterns of cytopenias

Cytopenias are a frequent and important side effect of CAR T-cell therapy, occurring across a wide range of CAR T-cell products, including those targeting CD19 and B-cell maturation antigen, as well as investigational products for a variety of conditions. However, comparisons of cytopenia rates between studies are complicated by variations in

Table 1. Hematotoxicity grading systems[20] and definitions of recovery phenotypes.

Grading system	Cytopenia	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE	Neutropenia	ANC <LLN 1,500/μL	ANC <1,500-1,000/μL	ANC <1,000-500/μL	ANC <500/μL
	Anemia	Hb <LLN 10 g/dL	Hb <10.0-8.0 g/dL	Hb <8.0 g/dL; transfusion	Life-threatening intervention
	Thrombocytopenia	Platelet count <LLN 75 g/L	<75-50 g/L	<50-25 g/L	<25 g/L
ICAHT	Early (day 0-30)	ANC <500/μL for 1-6 days	ANC <500/μL for 7-13 days	ANC <500/μL for ≥14 days ANC <100/μL* for ≥7 days**	ANC never above 500/μL ANC <100/μL for ≥14 days
	Late (after day +30)***	ANC <1,500/μL	ANC <1,000/μL	ANC <500/μL	ANC <100/μL
Phenotypes of neutrophil recovery	- Quick recovery: sustained neutrophil recovery without a second dip below an ANC <1,000/μL. - Intermittent recovery: neutrophil recovery (ANC >1,500/μL) followed by a second dip below an ANC <1,000/μL. - Aplastic recovery: continuous severe neutropenia (ANC <500/μL) for ≥14 days.				

*Profound neutropenia (absolute neutrophil count [ANC] <100/μL). **Protracted neutropenia (≥7 days). ***Non-transient neutropenia, see additional definitions from Liang *et al*. clarifying the necessary second measurement of ANC <1,500/μL within a certain time period. CTCAE: Common Terminology Criteria for Adverse Events; LLN: lower limit of normal; Hb: hemoglobin; ICAHT: immune effector cell-associated hematotoxicity.

definitions and differences in patient populations. In the pivotal clinical trials, rates of grade ≥3 neutropenia and grade ≥3 thrombocytopenia at any timepoint ranged from 13% to 90% and 9% to 60%, respectively (Figure 1A, B, *Online Supplementary Table S1*).[3-6,16,25-37] Similar rates were observed in retrospective observational studies.[20-22,38-40] Interpretation of long-term cytopenia across studies is challenging due to the aforementioned inconsistencies in definitions. In pivotal trials reporting cytopenias 1 month after T-cell infusion, rates of grade ≥3 neutropenia ranged from 13% to 40%, and thrombocytopenia from 4% to 32% (Figure 1C,D, *Online Supplementary Table S1*).[4-6,16,25,28,29,33,36,37,41] Prolonged grade ≥3 cytopenias occur at relatively lower rates, approximately 5%,[2] though available data are limited. Rejeski and colleagues identified three distinct patterns of neutrophil recovery following CAR T-cell therapy: transient cytopenias that resolve quickly ("quick"), biphasic or recurring cytopenias ("intermittent"), and an "aplastic" form associated with higher rates of morbidity and mortality (Table 1).[25] Findings from patients with LBCL treated with CAR T cells in the third-line setting indicate that approximately 40% experience a transient, quick-resolving form of neutropenia, while another 40% develop an intermittent pattern. The remaining 20% progress to

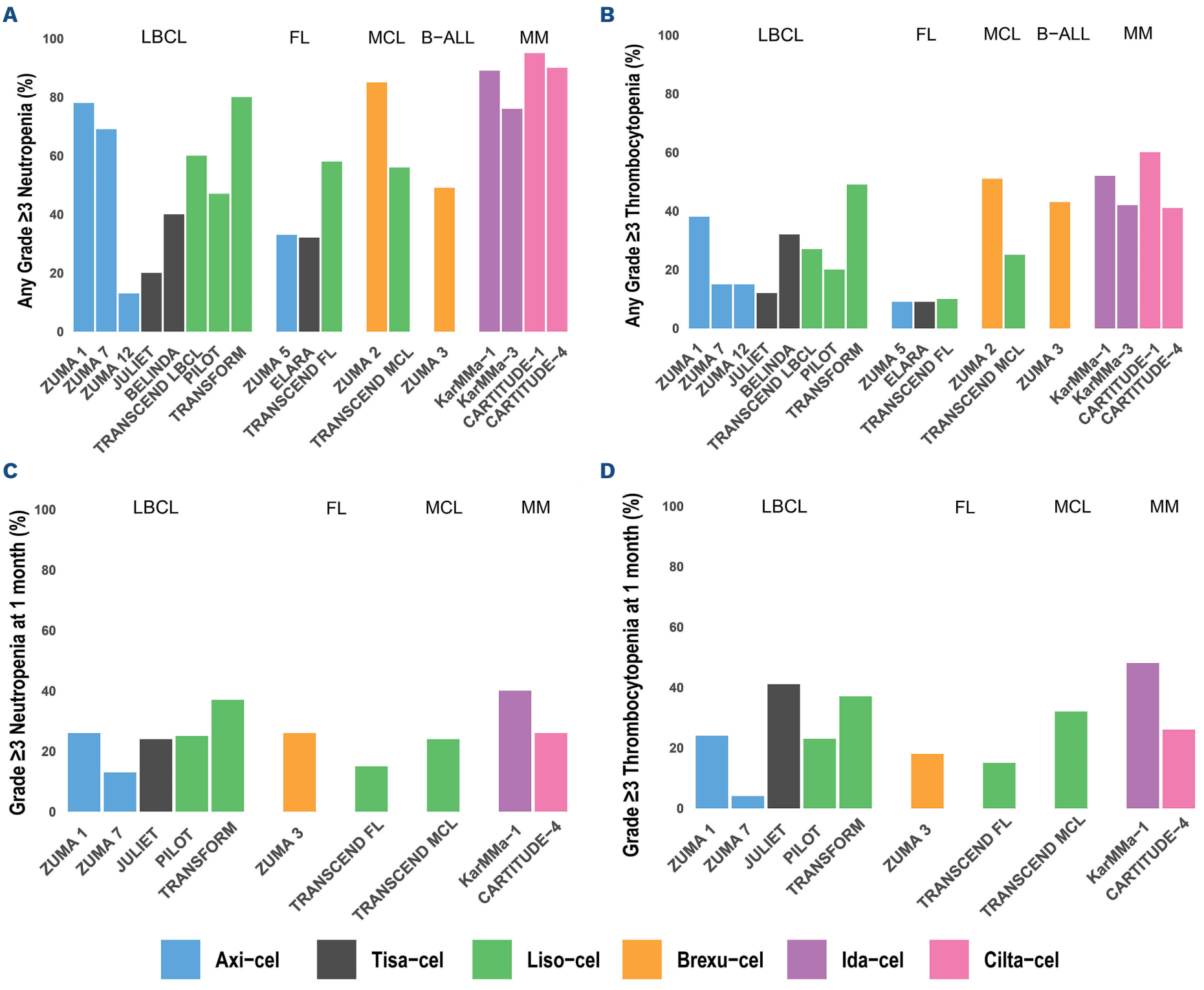

Figure 1. Grade ≥3 neutropenia and thrombocytopenia in the pivotal studies of chimeric antigen receptor T-cell therapies. (A) Any grade ≥3 neutropenia. (B) Any grade ≥3 thrombocytopenia. (C) Grade ≥3 neutropenia at 1 month. (D) Grade ≥3 thrombocytopenia at 1 month. The ZUMA 5 trial included patients with follicular and marginal zone lymphoma. LBCL: large B-cell lymphoma; FL: follicular lymphoma; MCL: mantle cell lymphoma; B-ALL: B cell acute lymphoblastic leukemia; MM: multiple myeloma; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Liso-cel: lisocabtagene maraleucel; Brexu-cel: brexucabtagene autoleucel; Ida-cel: Idecabtagene vicleucel; Cilta-cel: ciltacabtagene autoleucel.

a more severe aplastic form, which poses the greatest clinical challenges due to its prolonged course and significantly elevated risks of complications.[13,20,25] Notably, these patterns are specific to neutropenia, while thrombocytopenia and anemia follow different trajectories, with an often delayed nadir (end of month 1).

In acute myeloid leukemia, most CAR T cells are designed to target myeloid cells, which results in expected myeloid aplasia and necessitates consolidation with allogeneic stem cell transplantation (SCT). For example, in a recent study of 47 patients with acute myeloid leukemia treated with CLL1-directed CAR T cells, all experienced granulocytopenia, with 46 out of 47 developing grade 3/4 manifestations. Additionally, anemia was observed in 43 patients, and thrombocytopenia occurred in 44 patients, suggesting that hematologic toxicities are indeed a prominent and expected complication in the setting of myeloid disease.[42] Data on the incidence and nature of hematologic toxicities associated with CAR T-cell therapies in solid tumors are limited. In neuroblastoma patients, GD2-CAR T cells have been linked to significant hematologic toxicities, primarily due to lymphodepleting chemotherapy, with further exacerbation from the GD2-CAR T-cell therapy itself.[43] Notably, these adverse events were observed in all treated patients. Similarly, in a recent trial of HER-2 CAR T-cell therapy for sarcoma, 11 of 14 infused patients experienced grade 3/4 neutropenia.[44]

Clinical implications of early and late immune effector cell-associated hematotoxicity

Both early and late cytopenias impact the morbidity and mortality of patients receiving CAR T-cell therapies, partic-

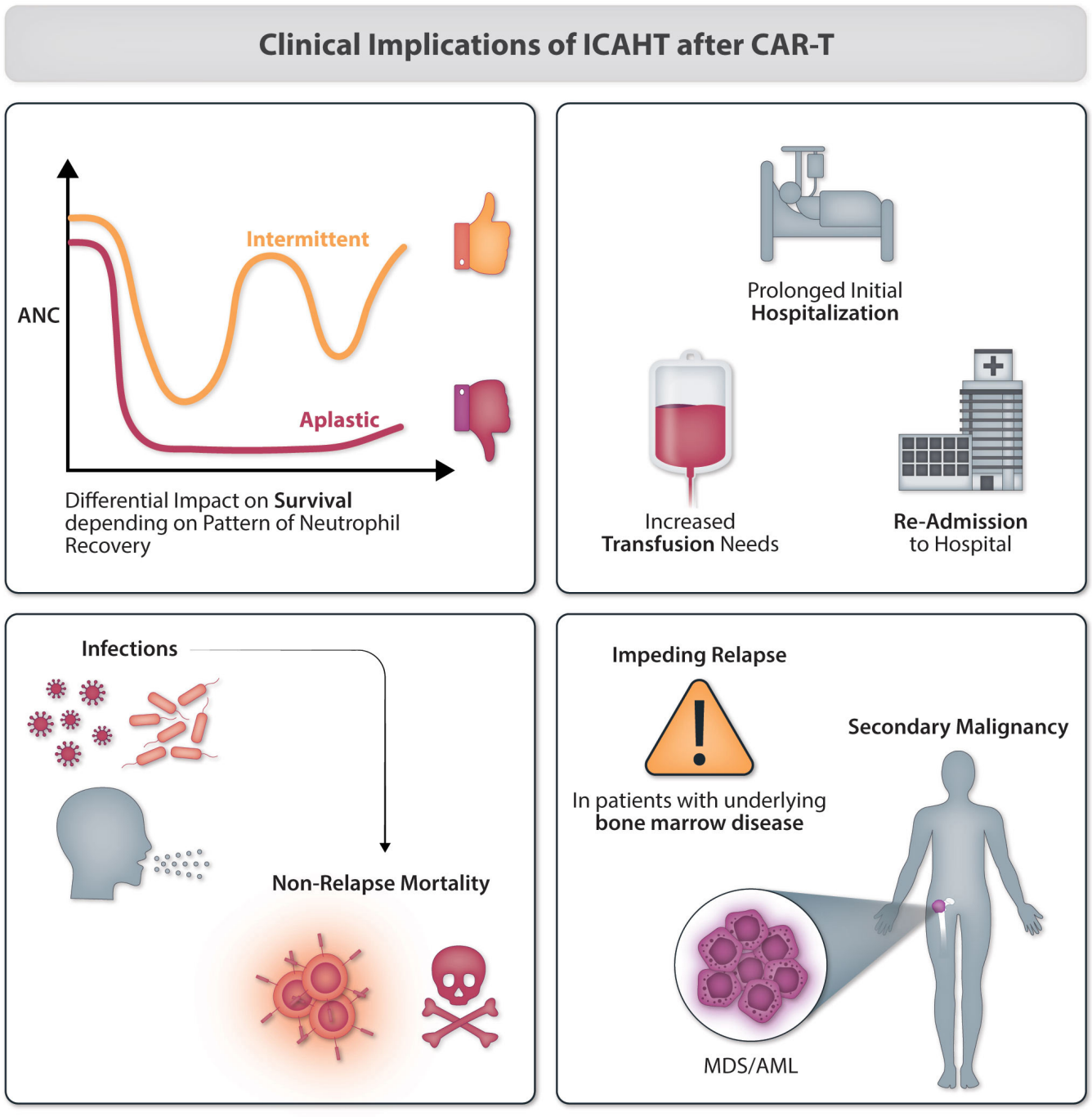

Figure 2. Clinical implications of immune effector cell-associated hematotoxicity after chimeric antigen receptor T-cell therapies. ANC: absolute neutrophil count; ICAHT: immune effector cell-associated hematotoxicity: CAR T: chimeric antibody receptor T-cell therapy; MDS: myelodysplatic syndrome; AML: acute myeloid leukemia.

ularly by shaping the risk of serious infectious complications (Figure 2).[15] Within the first 10 days after a CAR T-cell infusion, the majority of patients experience expected neutropenia likely primarily due to the lymphodepleting chemotherapy regimen. This typically consists of fludarabine at 25-30 mg/m^2 and cyclophosphamide at 250-500 mg/m^2 administered for 3 consecutive days, or bendamustine at a dose of 90 mg/m^2 for 2 days, leading to significant cellular immune suppression. This also represents the phase of coincident immunotoxicity (e.g., CRS or ICANS), which can necessitate the application of immunosuppressants such as high-dose corticosteroids or anti-inflammatory agents. Indeed, the majority of infections occur during this time of compounded immune suppression, with bacterial infections representing the dominant subtype.[9,20-22,26,27]

While most patients show initial cytotoxicity, the duration of the nadir phase defines the phenotype of neutrophil recovery (e.g., quick *vs*. intermittent *vs*. aplastic) and the subsequent risk of serious infection.[20] In a large cohort of patients with relapsed/refractory LBCL, those with brief neutrophil recovery followed by a second or multiple dips ("intermittent" phenotype) had comparatively low rates of infections and excellent survival outcomes.[25] On the other hand, patients with monophasic and extended severe neutropenia ("aplastic" phenotype) exhibited high rates of infections and poor treatment outcomes. Such extended cellular immunosuppression can predispose to bacterial infections, which predominate in the early phase of CAR T-cell therapy (until day +30).[9,15,28] While the overall incidence of fungal infections after CAR T-cell therapy is low,[29] cases of marked bone marrow aplasia can facilitate the development of invasive fungal disease including *Aspergillus*, *Fusarium*, or *Mucormycosis* infections, which all carry increased mortality in immunesuppressed CAR T-cell recipients.[30-32] Notably, "aplastic" patients (corresponding to grade 3/4 early ICAHT[33]) show much higher non-relapse mortality – the most devastating complication of CAR T-cell therapy.[25] Importantly, recent reports have highlighted that the main determinant of non-relapse mortality after CAR T-cell therapies are infections as opposed to the prototypical immune-related toxicities.[10,16] In addition, early hematotoxicity contributes to the duration of initial hospitalization as patients remain in hospital while receiving growth factor support or transfusions, particularly in the case of absent count recovery or concomitant infectious complications.[13] Late cytopenias (beyond day +30) manifest as either persistent bone marrow aplasia without antecedent count recovery or as recurrent cytopenia preceded by transient count recovery. The former can be particularly clinically challenging, as they represent a continuum of early ICAHT, are often refractory to multiple lines of treatment, and carry a high risk of infection. On the other hand, the latter are frequently clinically innocuous and are easily manageable with growth factor support or even a watch-and-wait approach. Of note, thrombocytopenia can follow a delayed trajectory and the nadir is commonly observed in the second month following CAR T-cell infusion.[20] Clinical implications of late ICAHT are related to the necessity of increased healthcare utilization due to transfusion support[17] or delayed infectious complications.[15] Persistently low blood counts can represent a harbinger of relapse or disease progression – especially in patients with underlying bone marrow disease. Since clinical trials often incorporate specific cytopenia thresholds as study exclusion criteria, cytopenic patients with progression after CAR T-cell therapy may also not be eligible for potentially efficacious post-relapse therapies. Perhaps the most important differential diagnoses of any new-onset or unexplained cytopenia are secondary myeloid malignancies, which are an emerging concern in the context of CAR T-cell therapies.[11,12,34,35] Concomitantly, close follow-up of blood counts should be advised in such patients and myeloid neoplasms should be ruled out by bone marrow examination when multilineage cytopenias persist over an extended period of time.

Risk factors associated with the development of cytopenias after chimeric antigen receptor T-cell therapy

The risk of developing cytopenias after CAR T-cell therapy can be broadly separated into treatment-, patient-, disease-, and CAR-T-cell-related features (Table 2). Each patient arrives at CAR T-cell treatment with a unique history of prior exposure to potentially myelotoxic treatments including chemotherapy, immunomodulatory agents and, in some cases, hematopoietic cell transplantation.[36,37] The administration of bridging therapies to control tumor growth during CAR T-cell manufacturing can impact hematopoietic function immediately prior to infusion and has been linked to the subsequent development of cytopenias and need for growth factor support.[38,39] Taken together, the extent of bone marrow function (as reflected by baseline cytopenias) appears to be a particularly strong risk factor for the development of post-CAR T-cell cytopenias. Other patient-related features to consider are the baseline state of systemic inflammation – reflected by elevations of serum C-reactive protein, interleukin-6, or ferritin.[25] More research efforts are needed to elucidate the contributing role of clonal hematopoiesis of indeterminate potential in CAR T-cell recipients.[40,41,45] However, preliminary findings by Hamilton and colleagues indicated that patients with extensive clonal expansion of the canonical genes associated with clonal hematopoiesis of indeterminate potential had reduced neutrophil count recovery, even when accounting for age and prior treatment exposure.[46] Clinicians should be on high alert for CAR T-cell-related immunotoxicity, including ICAHT, when patients present with high disease

Table 2. Risk factors associated with an increased incidence of cytopenias following chimeric antigen receptor T-cell therapy.

Type of factor	Risk factors	Additional comments	References
Treatment-related features	Number of prior therapy lines	Impact hematopoietic function and bone marrow reserve prior to CAR T-cell administration	Xia *et al.*[36] Penack *et al.*[67]
	Prior hematopoietic stem cell transplantation		Fried *et al.*[37] Zhou *et al.*[68]
	Administration of bridging therapies		Roddie *et al.*[39] Jain *et al.*[38]
Patient-related features	Pre-existing cytopenias	Particularly pre-existing thrombocytopenia	Rejeski *et al.*[20] Juluri *et al.*[58]
	Baseline inflammatory status	Increased serum ferritin and C-reactive protein	Rejeski *et al.*[20] Rejeski *et al.*[25]
Disease-related features	Underlying disease entity	B-ALL > B-NHL > MM > indolent lymphoma	Xia *et al.*[36] Rejeski *et al.*[33]
	Disease burden at time of CAR T-cell infusion (progressive disease, high LDH)	High marrow disease burden (particularly relevant in patients with MM and B-ALL)	Wudhikarn *et al.*[69] Logue *et al.*[70] Rejeski *et al.*[20,22,25] Brudno *et al.*[71] Nair *et al.*[47]
CAR T-cell-associated risk factors	Co-stimulatory molecule (CD28z > 41BB)	May also reflect differences in lymphodepletion (cyclophosphamide) dosing	Xia *et al.*[36] Rejeski *et al.*[33]
	Severe CRS and associated inflammatory patterns	Elevations of peak IL-6, IL-15, IL-18 and IFN-γ	Juluri *et al.*[58] Jain *et al.*[59] Zhou *et al.*[68] Frigault *et al.*[61] Rejeski *et al.*[25]
	Clonal T-cell expansion phenomena	T- and B-cell imbalance due to B-cell targeting CAR T cells	Rejeski *et al.*[65] Strati *et al.*[66]
	Active infection	Mainly viral or in case of concomitant sepsis	Pascutti *et al.*[72]
	CAR-HLH or IEC-HS	Cytopenia as an overlapping symptom	Sandler *et al.*[73] Hines *et al.*[74] Porter *et al.*[75]

CAR: chimeric antigen receptor; B-ALL: B-cell acute lymphoblastic leukemia; B-NHL: B-cell non-Hodgkin lymphoma; MM: multiple myeloma; LDH: lactate dehydrogenase; CRS: cytokine release syndrome; IL: interleukin; IFN: interferon; CAR-HLH: CAR-associated hemophagocytic lymphohistiocytosis; IEC-HS: immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome.

burden (e.g., rapidly rising or very elevated serum lactate dehydrogenase). This is especially relevant when underlying bone marrow infiltration is suspected in a lymphoma patient and/or in the case of increased marrow disease burden (e.g., increased blast percentage) in a patient with MM or B-cell precursor ALL.[21,22,25,47] Indeed, higher marrow blast percentages were associated with ICAHT severity in both pediatric and adult patients with B-cell precursor ALL.[47] Overall, the comparison of cytopenia incidence rates across disease entities is difficult due to the heterogeneity in reporting, patient populations, and study designs.[23] Nonetheless, a recent analysis applying the standardized ICAHT grading framework indicated that patients with mantle cell lymphoma showed the most extensive cytopenias (grade 3+: 28%), followed by those with LBCL (grade 3+: 23%) and MM (grade 3+: 15%).[33]

Importantly, the combination of baseline hyperinflammation and impaired hematopoietic reserve has been incorporated into a risk stratification tool termed CAR-HEMATOTOX, which is assessed prior to lymphodepletion (typically day -5). The score has been linked to extended cytopenia, increased healthcare utilization, infectious complications, and non-relapse mortality across a broad spectrum of disease indications including LBCL, mantle cell lymphoma, and MM.[20-22,27] Notably, the score also stratified for survival across diverse disease settings, highlighting the prognostic importance of systemic inflammation in CAR T-cell recipients.[48,49] An adapted version of the score replacing ferritin with bone marrow disease burden has been developed and validated for pediatric and adult patients with B-cell precursor ALL.[47] Additionally, the Endothelial Activation and Stress Index (EASIX) score, initially designed to assess endothelial dysfunction and predict survival in patients undergoing allogeneic SCT, has demonstrated utility in predicting CRS, ICANS, and survival in patients treated with CD19-targeting CAR T cells.[50-52] Recently, the association between EASIX and ICAHT was analyzed in MM patients treated with idecabtagene vicleucel, revealing an association with severe post-CAR T-cell cytopenias, further supporting the suggestion that endothelial activation may play a role in ICAHT.[53]

In terms of factors associated with the CAR T-cell product itself, CD28z-harboring CAR T cells (e.g., axicabtagene cilo-

leucel and brexucabtagene autoleucel) have been linked to protracted cytopenia compared with 41BBz CAR T-cells (e.g., tisagenlecleucel and lisocabtagene maraleucel).[36,54-58] On the one hand, this may reflect general differences in the dosing of the lymphodepleting chemotherapies (typically higher cyclophosphamide dose with axicabtagene ciloleucel). Alternative explanations relate to differential rates of severe CAR T-cell toxicities, especially increased CRS severity with CD28z CAR T-cell products. Indeed, CRS-related inflammatory patterns have been associated with prolonged cytopenias including peak elevations of systemic interleukin-6, interleukin-18, and interferon-γ.[25,37,58-61] This observation would be consistent with previous studies demonstrating that interferon-γ can impair the self-renewal of hematopoietic stem cells and skew their differentiation.[62,63] Additionally, the management of CRS or ICANS often involves the use of high-dose steroids and immunosuppressive agents such as anakinra. During this vulnerable phase, patients may also receive potentially myelotoxic co-medications, including anti-infective agents such as β-lactam antibiotics or sulfamethoxazole-trimethoprim. Some recent reports have implicated the expansion of oligoclonal (CAR) T-cell populations with T-cell receptor restriction – a mechanism for cytopenia that has also been described in cases of severe aplastic anemia and T-cell large granular lymphocytic leukemia.[64-66] For example, Strati and colleagues found that CAR T-cell recipients with prolonged cytopenia have increased frequencies of clonally expanded CX3CR1^{high} cytotoxic T cells that express high interferon-γ. Other potential differential diagnoses of early ICAHT to consider include viral infections, sepsis, hemophagocytic lymphohistiocytosis, and relapse of the underlying disease.

Pathophysiology of immune effector cell-associated hematotoxicity

The multitude of risk factors outlined above highlight that the underlying mechanism of ICAHT is unlikely to be related to one factor alone. Instead, the etiology of post-CAR T-cell cytopenia should be understood as multifactorial. These mechanisms have been summarized extensively in previous reviews.[13,76] Briefly, both the baseline state of chronic systemic inflammation and the hyperinflammation triggered by the migration of CAR T cells to the bone marrow, where they interact with target cells and induce localized inflammation, can lead to the secretion of cytokines and chemokines near stem cells, thereby impacting the self-renewal potential[62] and differentiation capacity of hematopoietic progenitors.[20,25,58,59,77] In addition, many patients already arrive at CAR T-cell therapy with impaired hematopoietic reserve due to prior exposure to chemotherapy and aging-related changes, which likely impacts the susceptibility to inflammatory-mediated stress.[36-39,67,68] Finally, the profoundly B-cell-depleting CAR T cells result in a dysbalance of T and B cells, favoring oligoclonal T-cell expansion.[65]

Importantly, differences have been observed between ICAHT phenotypes based on proteomic analysis of patients' serum collected at baseline and during the first month following CAR T-cell therapy.[25] The aplastic phenotype group exhibited higher levels of markers associated with endothelial dysfunction, inflammatory cytokines, macrophage activation, and T-cell suppression compared to the non-aplastic phenotype group. Gaining deeper fundamental understanding of the underpinnings of ICAHT may provide a foundation for investigating targeted interventions, such as interferon-neutralizing antibodies, like emapalumab, to potentially mitigate CAR-T-associated toxicities. However, it is still too early to determine whether this approach will effectively reduce CRS or alleviate hematologic toxicity and results of ongoing clinical trials are awaited (NCT06550141).

Future research efforts should focus on establishing preclinical models that adequately mirror the unique qualities of CAR-T related cytopenias. One of the most pressing questions with important clinical implications relates to understanding whether the inflammation-related changes within the bone marrow are truly induced by the CAR T cells themselves and reversible, or whether they more fundamentally represent fixed properties within the patients' pre-existing hematopoietic stem and progenitor cell compartment.

Considerations preceding lymphodepletion and chimeric antigen receptor T-cell infusion

In many CAR T-cell treatment centers, patients' baseline bone marrow reserve and inflammatory status are standardly assessed prior to initiating lymphodepleting chemotherapy. The use of the recently introduced and widely applied CAR-HEMATOTOX score, evaluating these parameters,[13,20] allows for early identification of patients at high risk of developing ICAHT. In such cases, proactive measures may be taken to mitigate this risk. One of these approaches involves the administration of granulocyte colony-stimulating factor (G-CSF) starting on day +2 after the CAR T-cell infusion. This early intervention aims to support bone marrow recovery and reduce the likelihood of severe neutropenia.[13] Another approach is based on modification of the lymphodepletion regimen. For instance, instead of the traditional combination of fludarabine and cyclophosphamide, bendamustine could be prescribed, given that it has been shown to be less myelosuppressive in some cases, which might reduce the risk of ICAHT in vulnerable patients.[78,79]

Additionally, for patients at significant risk, stem cell collection prior to the initiation of CAR T-cell therapy could be considered.[80] This involves harvesting and storing hematopoietic stem cells for potential use if the patient experiences prolonged bone marrow suppression or failure. However, this strategy presents logistical challenges, as it requires a spe-

cific and timely collection process, and not all patients may be eligible or able to undergo this procedure. Because the exact number needed to treat for such a strategy remains unclear, the health economic implications also need to be considered.[81] It remains to be studied whether concurrent collection of T cells (for CAR T-cell manufacturing) and stem cells (for back-up) is a possible strategy, although preliminary data suggest that it may be achievable from G-CSF-treated MM patients.[82]

Notwithstanding, the implementation of all these strategies requires careful evaluation of each patient's overall condition, including the ability to tolerate the proposed interventions and the feasibility of stem cell collection in the context of their disease and treatment timeline.

Management of immune effector cell-associated hematotoxicity

There are no prospective or randomized clinical trials specifically focused on ICAHT therapeutic approaches, and current recommendations are largely based on expert opinion.

Early cytopenias often resolve spontaneously, making a watch-and-wait approach reasonable. However, persistent grade 3/4 early ICAHT poses a significant clinical challenge, necessitating escalated therapeutic interventions.

Infection prophylaxis and management

Patients with both severe early and persistent late ICAHT face a high risk of infections, requiring comprehensive anti-infection prophylaxis. The ASTCT has recently issued detailed guidance for managing such patients.[83] These recommendations include the use of prophylactic antibiotics, antifungal, and antiviral agents, tailored to institutional protocols and adjusted based on patient-specific risk factors and local epidemiology. Regular monitoring for infection is essential, and if infection is suspected, infectious disease panel testing should be promptly initiated, followed by broad-spectrum antibiotic treatment as needed.

Transfusion support

A recent study analyzing 671 patients with aggressive lymphoma from the French DESCAR-T registry revealed that following CAR T-cell infusion, more than half of the cohort required at least one blood transfusion.[17] Specifically, 345 patients (51.4%) received red blood cell transfusions, and 280 patients (41.7%) required platelet transfusions. The greatest need for transfusion was documented within the first month after CAR T-cell infusion, with 359 patients (53.5%) requiring at least one transfusion during this period. Blood products are typically administered based on a patient's blood counts, and it is imperative that red blood cells and platelets be irradiated, in part because of the prior exposure to fludarabine, which can increase the risk of transfusion-associated graft-*versus*-host disease[84] (Table 3).

For red blood cell transfusion, a hemoglobin threshold of 7-8 g/dL is generally used for hemodynamically stable patients, while patients with cardiovascular diseases may require a higher threshold of 8 g/dL. Platelet concentrate transfusions are indicated for patients with platelet counts ≤10×10^9/L, or for those with active bleeding, fever, or ongoing infections, for whom the threshold is raised to ≤20×10^9/L. These transfusion thresholds are largely based on evidence from the SCT literature, as there is paucity of specific data for the setting of CAR T-cell therapy.

Beyond addressing immediate transfusion needs, attention should be be given to potential iron overload in patients receiving multiple red blood cell transfusions. Iron chelation therapy should be considered to prevent iron-induced organ damage, particularly in individuals requiring long-term transfusion support.

Granulocyte colony-stimulating factor

G-CSF is commonly administered after CAR T-cell therapy to reduce the duration of neutropenia and infection risk. However, its use in this setting requires careful consideration. A small retrospective study by Bindal *et al*. found that G-CSF administration within 30 days after CAR T-cell infusion was associated with poorer progression-free survival and overall survival.[85] These outcomes, however, are likely attributable to the underlying neutropenia rather than G-CSF use itself, as administration in these cases was reactive rather than prophylactic.

The timing of G-CSF administration is another important factor. Previous studies raised concerns that early administration of G-CSF might increase the risk of developing high-grade CRS.[86] Nevertheless, more recent evidence suggests that early G-CSF injection can be safe and does not necessarily exacerbate the severity of CRS. For example, a retrospective trial including 197 patients who received prophylactic G-CSF or PEGylated G-CSF prior to CAR T-cell infusion showed no significant increase in the progression from grade 1 CRS to higher grades.[87] Moreover, benefits, such as a faster neutrophil recovery and shorter duration of antibiotic use, were observed.

In the context of MM treatment using CAR T-cell products targeting B-cell maturation antigen (along with CD19 or CD138), a study by Ma *et al*. found no significant difference in the CRS severity between patients who did or did not receive G-CSF. However, there was an increased incidence of CRS in patients receiving cumulative doses of G-CSF greater than 1,500 μg or in those exposed to G-CSF administration for more than 5 days. This suggests that while G-CSF can be beneficial, its use should be carefully monitored to avoid potential complications.[88]

Patients with prolonged neutropenia after CAR T-cell therapy often receive G-CSF for extended periods, sometimes weeks to months. Currently, there are no definitive data on whether

G-CSF can be discontinued after 7-10 days, if no response is observed. There is no broad consensus as to whether to continue G-CSF administration even in the absence of an initial response, given the potential of delayed neutrophil recovery. The decision to continue (or discontinue) G-CSF should be tailored to each patient's response and overall clinical status, with consideration that prolonged administration may lead to persistent thrombocytopenia.[89]

Corticosteroids

Based on the pathophysiology of ICAHT, glucocorticoids may aid by suppressing excessive T-cell-mediated immune responses, reducing the production of autoantibodies, and promoting bone marrow hematopoiesis.[90] For patients with prolonged hematologic toxicity, particularly in the context of B-cell ALL after CAR T-cell therapy, low-dose oral prednisone (0.5 mg/kg/day) has been proposed as a treatment option, although evidence remains very circumstantial. In a small study by Wang *et al.*,[91] six out of 17 patients who initially responded to corticosteroids experienced a decrease in blood counts after corticosteroid withdrawal. Re-administration of corticosteroids resulted in a subsequent improvement in blood counts, suggesting the efficacy of these agents in managing late ICAHT when G-CSF fails.

Table 3. Supportive and therapeutic management of immune effector cell-associated hematotoxicity.

Intervention	Practical considerations	Recommendations	Disease	References
G-CSF	Day+2 or +5 following CAR T cells	Prophylaxis: Based on individual risk profile and institutional guidelines	Lymphoma	Liévin *et al.*[110] Miller *et al.*[87]
	Lack of response to G-CSF can help in identifying aplastic phenotypes	Therapeutic: Initiate when ANC <500/μl until ANC rises above this point.	Lymphoma MM	Galli *et al.*[111] Barreto *et al.*[112] Ma *et al.*[88] Miller *et al.*[87]
Red blood cell and platelet transfusions	Irradiated blood products; iron chelation may be considered	Based on individual risk profile as well as SCT and other institutional guidelines (no evidence specific to CAR T-cell therapy) Red blood cell concentrate: - Hemodynamically stable patients: hemoglobin threshold of 7-8 g/dL - Patients with cardiovascular disease: hemoglobin threshold of 8 g/dL Platelet concentrate: - Patients with platelet counts ≤10×10^9/L - Patients with active bleeding, febrile, or active infections: platelet counts ≤20×10^9/L	-	Sureda *et al.*[113] Carson *et al.*[114] Schiffer *et al.*[115]
Stem cell boost	Autologous stem cells - mostly unavailable in lymphoma patients	If autologous cells are available, their use should be considered for every patient with an aplastic phenotype (grade 3 or higher early ICAHT refractory to G-CSF) beyond day +14, or in select cases of persistent intermittent neutropenia	Lymphoma B-ALL MM	Gagelmann *et al.*[80] Mullanfiroze *et al.*[98] Rejeski *et al.*[99] Davis *et al.*[116] Mohan *et al.*[117]
	Allogeneic SCT - most patients are not appropriate candidates	-	-	-
Alternative treatment strategies with lower levels of evidence				
TPO mimetics	Not to be taken together with dairy products	Initiate in cases of prolonged thrombocytopenia requiring repeated platelet transfusions, i.e., 2 or more units of platelets in a 7-day timespan	Lymphoma MM B-ALL	Baur *et al.*[118] Beyar-Katz *et al.*[93] Drillet *et al.*[94] Wesson *et al.*[95] Mingot-Castellano *et al.*[97]
Corticosteroids	-	Low-dose oral prednisone (0.5 mg/kg/day) beyond day 30	B-ALL	Wang *et al.*[91]
High-dose IVIG	-	2 g/kg given in divided doses over 4-5 days	Lymphoma	Laham *et al.*[119]
Sirolimus	-	-	Lymphoma	Xing *et al.*[120]

G-CSF: granulocyte colony-stimulating factor; CAR: chimeric antigen receptor; ANC: absolute neutrophil count; MM: multiple myeloma; SCT: stem cell transplantation; ICAHT: immune effector cell-associated hematotoxicity; B-ALL: B-cell acute lymphoblastic leukemia; TPO: thrombopoietin; IVIG: Intravenous immunoglobulin.

Thrombopoietin receptor agonists

Thrombocytopenia following CAR T-cell therapy can be severe and prolonged, often requiring repeated platelet transfusions, especially in patients with the ”aplastic” phenotype. The occurrence of bleeding in these patients is underreported and should be further evaluated in prospective clinical trials. Thrombopoietin receptor agonists, such as eltrombopag and romiplostim, are potential treatment options for patients with persistent thrombocytopenia after CAR T-cell therapy, as they stimulate platelet production and may reduce transfusion dependence. They are also thought to promote the reconstitution of neutrophil counts.[92,93] While several retrospective studies have shown favorable responses to these agents, no prospective randomized trials have been conducted to validate these findings and the retrospective studies have uniformly lacked a control arm employing the watch-and-wait approach.[92,94-96] The largest study to date, in which 42 patients were treated with eltrombopag because of persistent, high-grade leukopenia and/or thrombocytopenia after CAR T-cell therapy, showed encouraging outcomes, with 94% experiencing recovery from cytopenias within 180 days.[95] A multicenter retrospective analysis from a Spanish group reported that, among 38 patients with platelet transfusion dependence at day +30 or beyond following CAR T-cell infusion, 76.3% (29 patients) achieved platelet transfusion independence after a median of 32 days of eltrombopag treatment. Additionally, 82.6% of patients with severe neutropenia and 82.9% of those dependent on red blood cell transfusions recovered after a median of 22 and 29 days, respectively.[97] Both studies found that eltrombopag was well-tolerated, with no major toxicities observed, suggesting the efficacy of this treatment option for managing post-CAR T-cell cytopenias. However, it is unclear what the natural time course of platelet recovery would have been without the administration of thrombopoietin receptor agonists and further investigation is needed to confirm the long-term safety and efficacy of these drugs.

Hematopoietic stem cell boost

Autologous stem cell boost

For patients with G-CSF-refractory and persistent ICAHT, an autologous stem cell boost is emerging as a promising therapeutic option. This approach is particularly valuable in patients for whom pre-collected stem cells available. However, a large worldwide survey showed that even in patients with a prior history of autologous SCT, a stem cell boost was either available in less than 30% of patients or unavailable at all (61% of survey responders).[23]

Data from multicenter, retrospective studies in the context of CAR T-cell therapy targeting CD19 and B-cell maturation antigen indicate that autologous stem cell boosts can lead to rapid and significant hematologic recovery (*Online Supplementary Table S2*). The median dose of $CD34^+$ cells used ranges from 2.75 to 6.75×10^6/kg, although the optimal dose for ICAHT treatment is still unknown. Remarkably, 70-100% of patients receiving a stem cell boost experience complete recovery of neutrophils and, in many cases, of platelets. The responses typically occur within 7-21 days after infusion, and the procedure is generally safe, with no need for conditioning therapy. Only one patient has been reported to have developed a second episode of CRS following the boost.[98] While this strategy is utilized in MM patients, from whom stem cells are collected routinely, it is less commonly feasible for patients with other diseases. The main challenges include the availability of stored autologous stem cells and the potential, albeit unproven, risk of tumor cell contamination in the stem cell product.

Allogeneic stem cell transplantation

In cases in which autologous stem cells are not available, allogeneic SCT may be considered, although this option is typically reserved for patients who have exhausted other treatment options and are not critically ill. Reports, mainly concerning patients with ALL, suggest that allogeneic SCT can be safe, with no significant incidence of graft-*versus*-host disease.[98,99] However, due to the severity of the condition in these patients, many of them cannot be offered this therapeutic option.

Hematologic toxicities in patients receiving bispecific antibodies

Hematologic toxicities are an established complication in CAR T-cell therapy, but their emergence in patients receiving bispecific antibodies (BsAb) is becoming increasingly recognized.[100,101] Currently, the term ICAHT has been specifically applied to describe hematologic toxicities in the context of CAR T-cell therapy. Because the ICAHT grading has not yet been broadly applied for BsAb, it remains difficult to contextualize the clinical significance of hematologic toxicities with this treatment modality. The currently used CTCAE grading, which relies on one-time measurements below certain thresholds, may overestimate the clinical impact of cytopenias.

BsAb, which bridge CD3 on T cells with tumor-associated antigens on malignant cells, have demonstrated significant efficacy across various hematologic malignancies. However, their use is accompanied with a notable incidence of hematological toxicities. Overall, grade 3 neutropenia has been described in about 25% of patients, with grade 3 thrombocytopenia occurring in between 2% to 14% of lymphoma patients treated with CD20xCD3 bispecific T-cell engager therapy.[102-105] In patients with MM, the BsAb-related bone marrow toxicity is much greater than that observed with BsAb in the lymphoma setting, with 40%-60% of MM patients developing severe neutropenia and 20% experiencing severe thrombocytopenia.[106-109] BsAb-related

hematologic toxicities can present as severe and prolonged cytopenias, which may be resistant to conventional supportive measures such as G-CSF administration. The underlying pathophysiology is not fully understood, but it is believed to involve sustained T-cell activation and cytokine release, leading to bone marrow suppression. Managing hematologic toxicities in patients undergoing BsAb therapy can be challenging, particularly due to the limited data on effective treatments and the heavily pretreated nature of these patients, many of whom have also received prior CAR T-cell therapy. Unlike CAR T-cell therapy, BsAb therapy can be withheld or given over a prolonged time frame, allowing such toxicities to be reduced. In contrast to CAR T-cell therapy, where autologous stem cell boosts have shown potential in mitigating ICAHT, such approaches have not been validated in the BsAb therapy setting. Thus, further research is needed to understand the true clinical significance of ICAHT with BsAb and to develop evidence-based guidelines for its management, aiming to minimize hematologic toxicity, while maintaining the therapeutic efficacy of these drugs.

Conclusions and future perspectives

Hematologic toxicities, particularly ICAHT, present a significant challenge in CAR T-cell therapy, affecting both the short- and long-term outcomes of patients. The incidence and severity of cytopenias are influenced by factors such as the type of the CAR T-cell product, disease burden, and conditioning protocols. While transient cytopenias are common, prolonged and biphasic forms pose greater risks, including life-threatening infections, transfusion dependency, and increased non-relapse mortality. Early identification, standardized grading, and individualized management strategies are essential to mitigate these toxicities. Greater understanding of different mechanisms underlying different manifestations of hematotoxicity will be essential to develop next-generation treatment strategies.

ICAHT treatment is multifaceted, including supportive therapies such as G-CSF, platelet and red blood cell transfusions, with emerging evidence on the use of corticosteroids and thrombopoietin receptor agonists. Stem cell boosts, when available, are often the most effective option. The choice of treatment should be tailored to each patient's condition, prior response to therapies, and resource availability. Additionally, infection prophylaxis is a critical component of care for these patients. As CAR T-cell therapy expands to new indications in both malignant and non-malignant conditions, ongoing research is essential to refine the strategies, optimize protocols, and ultimately improve patients' survival and quality of life.

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Contributions

All the authors contributed equally to the analysis of the literature, writing and editing of the manuscript and approved the final version of the paper.

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Data-sharing statement

The data on which this review is based are available upon request.

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