haematologica
Journal of the Ferrata Storti Foundation

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by Ofrat Beyar-Katz, Kai Rejeski and Roni Shouval

Received: November 13, 2024.
Accepted: February 7, 2025.

Citation: Ofrat Beyar-Katz, Kai Rejeski and Roni Shouval. Immune effector cell-associated hematotoxicity: mechanisms, clinical manifestations, and management strategies. Haematologica. 2025 Feb 20. doi: 10.3324/haematol.2024.286027 [Epub ahead of print]

Review

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

Ofrat Beyar-Katz[1,2*], Kai Rejeski[3,4,5*] and Roni Shouval[3,6*]

*All authors contributed equally to this work

[1]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel; [2]The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; [3]Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA; [4]Department of Medicine III – Hematology/Oncology, LMU University Hospital, LMU Munich, Munich, Germany; [5]Bavarian Cancer Research Center (BZKF), partner site Munich, Munich, Germany; [6]Department of Medicine, Weill Cornell Medical College, New York, NY, USA

Running title: Immune Effector Cell-Associated Hematotoxicity

Declaration of Interests:

O.B-K. declares no competing interests.

K.R. Kite/Gilead: Research Funding, Consultancy, Honoraria and travel support; Novartis: Honoraria; BMS/Celgene: Consultancy, Honoraria; Pierre-Fabre: travel support.

R.S. received speaker honorarium from Incyte.

Corresponding author:

Ofrat Beyar-Katz, MD, PhD

Department of Hematology and Bone Marrow Transplantation

Rambam Health Care Campus

8, Ha'Aliya Street

Haifa 3109601, Israel

Tel: +972-544980188
Fax: +972-47772343
E-mail: o_katz@rmc.gov.il

Author Contribution Statement

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.

Funding:

O.B-K: reports grant support from the Israel Science Foundation (696/23), the Israel Cancer Association (2024009) and the Dahlia Greidinger Anti-Cancer Fund.

KR received a fellowship from the School of Oncology of the German Cancer Consortium (DKTK) and was funded by the Else Kröner Forschungskolleg (EKFK) within the Munich Clinician Scientist Program (MCSP). This work was further supported by a grant from the Bruno and Helene Jöster Foundation (to KR) and the “CAR-T Control” translational group within the Bavarian Center for Cancer Research (BZKF-#TLG-22) (to KR).

RS reports grant support from an NIH-NCI K08CA282987, NIH-NCI Memorial Sloan Kettering Cancer Center Support Grant (P30 CA008748), the Long Island Sound Chapter, Swim Across America, the Robert Hirschhorn Award, and Comedy vs. Cancer.

Acknowledgments

The authors wish to acknowledge with thanks the assistance of Sonia Kamenetsky in the preparation of this manuscript.

Data sharing statement

The data is available upon request.

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, patient immune status, and CAR-T product features. Standardized grading systems, based on the depth and duration of neutropenia, have improved ICAHT classification 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 CAR-T efficacy. As CAR-T therapy broadens to new indications, optimized ICAHT management could enhance patient outcomes, reduce healthcare utilization, and increase therapy accessibility.

Keywords: CAR-T cell therapy, immune effector cell-associated hematotoxicity (ICAHT), hematopoietic stem cell boost, granulocyte colony-stimulating factor (G-CSF)

Introduction

Chimeric antigen receptor (CAR)-T cell therapy has transformed the treatment of hematological malignancies, offering durable remissions in patients with otherwise refractory disease. Since its initial approval for B-cell acute lymphoblastic leukemia (ALL), CAR-T therapy has expanded to multiple indications, including large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and multiple myeloma. 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 product[3-6], disease burden[7], cytokine profile[8], as well as multiple factors reviewed elsewhere[2,8]. Beyond CRS and ICANS, CAR-T 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 patient management and long-term outcomes[2].

Hematotoxicity, also referred to as immune effector cell-associated hematotoxicity (ICAHT)[13], represents 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 therapy, severely impair the host immune system's ability to combat bacterial, fungal, and viral pathogens[9,14,15]. This immunosuppressive state is further exacerbated by B-cell aplasia and hypogammaglobulinemia - frequent off-target effects of B-cell-directed CAR-T therapies - that 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 CAR-T-treated patients across diverse clinical settings[10,16]. Moreover, the development of transfusion dependency[17] adds to therapy-related

morbidity, extends hospitalization, and imposes a substantial burden on healthcare resources.

This review will focus on the hematological toxicities associated with CAR-T therapy. We will examine the frequency, pathophysiology, clinical consequences, and approaches to managing these toxicities. Furthermore, we will explore potential strategies to reduce their occurrence and discuss the implications for improving patient 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 now improve the accuracy of toxicity reporting and facilitate 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 hematological toxicities, particularly cytopenias, have evolved. Although clinical trials primarily follow the Common Terminology Criteria for Adverse Events (CTCAE, Table 1), this system does not fully capture the unique patterns of cytopenias seen after CAR-T 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 therapy, the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) have 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 hematological

toxicities in CAR-T 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 Cytopenia

Cytopenias are a frequent and important side effect of CAR-T cell therapy, occurring across a wide range of CAR-T products, including those targeting CD19 and B-cell maturation antigen (BCMA), as well as investigational products for a variety of conditions. However, comparisons of cytopenia rates between studies are complicated by variations in definitions and differences in patient populations. In the pivotal clinical trials, rates of grade ≥3 neutropenia and grade ≥3 thrombocytopenia at any time point ranged from 13% to 90% and 9% to 60%, respectively (Figure 1A-B, Supplemental 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 one month after infusion, rates of grade ≥3 neutropenia ranged from 13% to 40%, and thrombocytopenia from 4% to 32% (Figure 1C-D, Supplemental 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 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 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 specifically

address neutropenia, while thrombocytopenia and anemia follow different trajectories, with an often delayed nadir (end of month 1).

In acute myeloid leukemia (AML), 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 AML patients 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 hematological toxicities are indeed a prominent and expected complication in the setting of myeloid disease[42].

Data on the incidence and nature of hematological toxicities associated with CAR-T cell therapies in solid tumors are limited. In neuroblastoma patients, GD2-CAR-T cells have been linked to significant hematological toxicities, primarily due to lymphodepleting chemotherapy, with further exacerbation by GD2-CAR-T therapy[43]. Notably, these adverse events were observed in all treated patients. Similarly, in a recent trial of HER-2 CAR-T cells for sarcoma, 11 of 14 infused patients experienced grade 3-4 neutropenia[44].

Clinical Implications of Early and Late ICAHT

Both early and late cytopenias impact the morbidity and mortality of patients receiving CAR-T cell therapies, particularly by shaping the risk for serious infectious complications (Figure 2)[15]. Within the first 10 days after 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/m² and cyclophosphamide at 250-500 mg/m² administered for three consecutive days, or bendamustine at a dose of 90 mg/m² for two 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 for serious infection[20]. In a large relapsed/refractory LBCL cohort, patients 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 CAR-T phase (until day +30)[9,15,28]. While the overall incidence of fungal infections after CAR-T therapy is low[29], cases of marked bone marrow (BM) aplasia can facilitate the development of invasive fungal disease including Aspergillus, Fusarium, or Mucormycosis infections, which all carry increased mortality in immune suppressed CAR-T recipients[30-32]. Notably, "aplastic" patients (corresponding to grade 3-4 early ICAHT[33]) show much higher non-relapse mortality (NRM) – the most devastating complication of CAR-T therapy[25]. Importantly, recent reports have highlighted that the main determinant of NRM after CAR-T 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 case of absent count recovery or concomitant infectious complications[13].

Late cytopenias (beyond day +30) manifest as either persistent BM 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 infection risk. 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 infusion[20]. Clinical implications of late ICAHT relate to the necessity of increased health care utilization due to transfusion support[17] or delayed infectious complications[15]. Persistently low counts can represent a harbinger of relapse or disease progression

– especially in patients with underlying BM disease. Since clinical trials often incorporate specific cytopenia thresholds as study exclusion criteria, cytopenic patients with progression after CAR-T therapy may also not be eligible for potentially efficacious post-relapse therapies. Perhaps the most important differential diagnosis 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 BM examination when multilineage cytopenias persist over an extended period of time.

Risk Factors Associated with the Development of Cytopenias after CAR-T

The risk of developing cytopenias after CAR T-cell therapy can broadly be separated into treatment-, patient-, disease-, and CAR-T related features (Table 2). Each patient presents to CAR-T 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 manufacturing can impact hematopoietic function immediately prior to infusion and has been linked to the subsequent development of cytopenia and need for growth factor support[38,39]. Taken together, the extent of BM function (as reflected by baseline cytopenias) appears to be a particularly strong risk factor for the development of post-CAR-T cytopenias. Other patient-related features to consider are the baseline state of systemic inflammation – reflected by elevations of serum C-reactive protein, IL-6, or ferritin[25]. More research efforts are needed to elucidate the contributing role of clonal hematopoiesis of indeterminant potential (CHiP) in CAR-T recipients[40,41,45]. However, preliminary findings by Hamilton and colleagues indicated that patients with extensive clonal expansion of canonical CHiP genes had reduced neutrophil count recovery, even when accounting for age and prior treatment exposure[46]. Clinicians should be at high alert for CAR-T related immunotoxicity including ICAHT when patients present with high disease burden (e.g., rapidly rising or very elevated serum LDH). This is especially relevant when underlying BM infiltration is suspected in a lymphoma patient and/or in case of increased marrow disease burden (e.g., increased blast percentage) in a patient with multiple myeloma or B-cell precursor acute lymphoblastic leukemia (B-ALL)[21,22,25,47]. Indeed, higher marrow blast

percentages were associated with ICAHT severity in pediatric and adult B-ALL patients[47]. Overall, the comparison of cytopenia incidence rates across disease entities is difficult due to the heterogeneity in reporting, patient populations, and study design[23]. Nonetheless, a recent analysis applying the standardized ICAHT grading framework indicated that MCL patients showed the most extensive cytopenias (G3+: 28%), followed by LBCL (G3+: 23%) and multiple myeloma (G3+: 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 NRM across a broad spectrum of disease indications including LBCL, MCL, and multiple myeloma[20-22,27]. Notably, the score also stratified for survival across diverse disease settings, highlighting the prognostic importance of systemic inflammation in CAR-T recipients[48,49]. An adapted version of the score replacing ferritin with BM disease burden has been developed and validated for pediatric and adult patients with B-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 has been analyzed in multiple myeloma patients treated with ide-cel, revealing an association with severe post-CAR-T cytopenias, further supporting the suggestion that endothelial activation may play a role in ICAHT[53].

In terms of factors associated with the CAR-T product itself, CD28z-harboring CAR-T cells (e.g., axi-cel and brexu-cel) have been linked to protracted cytopenia compared with 41BBz CAR T-cells (e.g., tisa-cel and liso-cel)[36,54-58]. On the one hand, this may reflect general differences in the dosing of the lymphodepleting chemotherapies (typically higher cyclophosphamide dose with axi-cel). Alternative explanations relate to differential rates of severe CAR-T toxicities, especially increased CRS severity with CD28z CAR-T products. Indeed, CRS-related inflammatory patterns have been associated with prolonged cytopenias including peak elevations of systemic

interleukin [IL]-6, IL-18, and interferon [IFN]-γ[25,37,58-61]. This observation would be consistent with previous studies demonstrating that IFN-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 like anakinra. During this vulnerable phase, patients may also receive potentially myelotoxic co-medications, including anti-infective agents such as beta-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 recipients with prolonged cytopenia exhibit increased frequencies of clonally expanded CX3CR1^{high} cytotoxic T cells that express high IFN-γ. Other potential differential diagnoses of early ICAHT to consider include viral infections, sepsis, HLH, and relapse of the underlying disease.

Pathophysiology of ICAHT

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 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 CAR T-cell migration 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 present to CAR-T therapy with impaired hematopoietic reserve due to prior chemotherapy exposure 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 patient serum collected at baseline and during the first month following CAR-T 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 IFN-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 hematological 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 if the inflammation-related changes within the BM are truly induced by the CAR T-cells themselves and reversible, or if they more fundamentally represent fixed properties within the patients' pre-existing HSPC compartment.

Considerations preceding lymphodepletion and CAR-T cell infusion

At multiple CAR-T cell treatment centers, patient's baseline BM 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 ICAHT development. In such cases, proactive measures may be taken to mitigate this risk. One of these approaches involves the administration of G-CSF starting on day +2 post-CAR-T cell infusion. This early intervention aims to support BM recovery and reduce the likelihood of severe neutropenia[13]. Another approach is based on the 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 ICAHT risk in vulnerable patients[78,79].

Additionally, for patients at significant risk, stem cell collection prior to CAR-T therapy initiation could be considered[80]. This involves harvesting and storing hematopoietic

stem cells for potential use if the patient experiences prolonged BM suppression or failure. However, this strategy presents logistical challenges, as it requires a specific 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 if concurrent collection of T cells (for CAR-T manufacturing) and stem cells (for back-up) is a possible strategy, though preliminary data suggest it may be achievable from G-CSF treated multiple myeloma 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 ICAHT

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 American Society for Transplantation and Cellular Therapy (ASTCT) has recently issued detailed guidance for managing such patients[83]. These recommendations include the use of prophylactic antibiotics, antifungals, and antivirals, 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 (RBC) transfusions, and 280 patients (41.7%) required platelet transfusions. The greatest need for transfusion was documented within the first month post-CAR-T cell infusion, with 359 patients (53.5%) requiring at least one transfusion during this period. Blood products are typically administered based on patient's blood counts, and it is imperative that RBCs and platelets be irradiated partially due to the prior exposure to fludarabine, which can increase the risk of transfusion-associated graft-versus-host disease (TA-GvHD)[84] (Table 3).

For RBC 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□/L, or for those with active bleeding, fever, or ongoing infections, where the threshold is raised to ≤20 × 10□/L. These transfusion thresholds are largely based on evidence from the stem cell transplantation literature, as there is paucity of specific data for the CAR-T therapy setting.

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

G-CSF

G-CSF is commonly administered after CAR-T therapy to reduce neutropenia duration and infection risk. However, its use in this setting requires careful consideration. A small retrospective study by Bindal et al. reported that G-CSF administration within 30 days post-CAR-T infusion was associated with poorer progression-free survival (PFS) and overall survival (OS)[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 application 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 CRS severity. For example, a retrospective trial including 197 patients who received prophylactic G-CSF or PEGylated G-CSF prior to CAR-T 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 multiple myeloma treatment using CAR-T products targeting BCMA (along with CD19 or CD138), a study by Ma et al. found no significant difference in the CRS severity between patients who did and did not receive G-CSF. However, there was an increased incidence of CRS in patients receiving cumulative doses of G-CSF greater than 1500 μg or in those exposed to G-CSF administration for more than five 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 therapy often receive G-CSF for extended periods, sometimes lasting 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 wide 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 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 hematological toxicity, particularly in the context of B-ALL post-CAR-T 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], 6 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.

TPO 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 post-CAR-T 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, where 42 patients were treated with eltrombopag due to persistent high-grade leukopenia and/or thrombocytopenia post-CAR T-cell therapy, showed encouraging outcomes, with 94% experiencing recovery from cytopenias within 180 days[95]. A multicenter retrospective analysis from the Spanish group reported that, among 38 patients with platelet transfusion dependence at day +30 or beyond following CAR-T 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 with RBC transfusion dependence recovered after a median of 22 and 29 days, respectively[97]. Both studies reported that eltrombopag was well-tolerated, with no major toxicities observed, suggesting the efficacy of this treatment option for managing post-CAR-T cytopenias. However, it is unclear what the natural time course of platelet recovery would have been without the administration of TPO agonists and further investigation is needed to confirm its long-term safety and efficacy.

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 who have pre-collected stem cells available. However, a large worldwide survey showed that even in patients with a prior history of autologous SCT, 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 therapy targeting CD19 and BCMA indicate that autologous stem cell boosts can lead to rapid and significant hematological recovery (Supplemental Table S2). The median dose of CD34-positive 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 post-infusion, and the procedure is generally safe, with no need for conditioning therapy. Only one patient has been reported to develop a second episode of CRS following the boost[98]. While this strategy is utilized in multiple myeloma patients, where stem cell collection is routinely performed, 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 where 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 in ALL, suggest that allogeneic SCT can be safe, with no significant incidence of GvHD[98,99]. However, due to the severity of the condition in these patients, many of them cannot be offered this therapeutic option.

Hematological toxicities in patients receiving bispecific antibodies

Hematological toxicities are an established complication in CAR-T cell therapy, but its emergence in patients receiving bispecific antibodies (BsAb) is becoming

increasingly recognized[100,101]. Currently, the term ”ICAHT” has been specifically applied to describe hematological toxicities in the context of CAR-T therapy. Because the ICAHT grading has not yet been broadly applied for BsAb, it remains difficult to contextualize the clinical significance of hematological 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 hematological malignancies. However, their use is accompanied with notable incidence of hematological toxicities. Overall, grade 3 neutropenia is described in about 25% of patients, with grade 3 thrombocytopenia ranging between 2% to 14% in lymphoma patients treated with CD20 CD3 bispecific T-cell engager therapy[102-105]. In patients with multiple myeloma, the BsAb-related BM toxicity is much higher compared to that observed with BsAb in the lymphoma setting, with 40%-60% of multiple myeloma patients developing severe neutropenia and 20% experiencing severe thrombocytopenia[106-109]. BsAb-related hematological 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 BM suppression. Managing hematological 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 therapy, BsAb therapy can be withheld or given over a prolonged time frame, allowing to reduce such toxicities. In contrast to CAR-T therapy, where autologous stem cell boosts have shown a 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 bispecifics and to develop evidence-based guidelines for its management, aiming to minimize hematological toxicity, while maintaining the therapeutic efficacy of these drugs.

Conclusions and Future Perspectives

Hematological toxicities, particularly ICAHT, present a significant challenge in CAR-T cell therapy, affecting both short- and long-term patient outcomes. The incidence and severity of cytopenias are influenced by factors such as the CAR-T product type, 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. More foundational 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 RBC transfusions, with emerging evidence on the use of corticosteroids and TPO 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 therapy expands to new indications in both malignant and non-malignant conditions, ongoing research is essential to refine these strategies, optimize protocols, and ultimately improve patient survival and quality of life.

References:

1. Muller F, Taubmann J, Bucci L, et al. CD19 CAR T-Cell Therapy in Autoimmune Disease - A Case Series with Follow-up. N Engl J Med. 2024;390(8):687-700.
2. Brudno JN, Kochenderfer JN. Current understanding and management of CAR T cell-associated toxicities. Nat Rev Clin Oncol. 2024;21(7):501-521.
3. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
4. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-2544.
5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
6. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021;398(10299):491-502.
7. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol. 2021;39(35):3978-3992.
8. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2022;22(2):85-96.
9. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood. 2018;131(1):121-130.
10. Cordas Dos Santos DM, Tix T, Shouval R, et al. A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy. Nat Med. 2024;30(9):2667-2678.
11. Tix T, Alhomoud M, Shouval R, et al. Second primary malignancies after CAR T-cell therapy: A systematic review and meta-analysis of 5,517 lymphoma and myeloma patients. Clin Cancer Res. 2024;30(20):4690-4700.

12. Storgard R, Rejeski K, Perales MA, Goldman A, Shouval R. T-Cell Malignant Neoplasms After Chimeric Antigen Receptor T-Cell Therapy. JAMA Oncol. 2024;10(6):826-828.
13. Rejeski K, Subklewe M, Aljurf M, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142(10):865-877.
14. Rejeski K, Perez A, Iacoboni G, et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL. J Immunother Cancer. 2022;10(5):e004475.
15. Kampouri E, Little JS, Rejeski K, Manuel O, Hammond SP, Hill JA. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. Transpl Infect Dis. 2023;25 Suppl 1:e14157.
16. Lemoine J, Bachy E, Cartron G, et al. Nonrelapse mortality after CAR T-cell therapy for large B-cell lymphoma: a LYSA study from the DESCAR-T registry. Blood Adv. 2023;7(21):6589-6598.
17. Vic S, Thibert JB, Bachy E, et al. Transfusion needs after CAR T-cell therapy for large B-cell lymphoma: predictive factors and outcome (a DESCAR-T study). Blood Adv. 2024;8(6):1573-1585.
18. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
19. Pennisi M, Jain T, Santomasso BD, et al. Comparing CAR T-cell toxicity grading systems: application of the ASTCT grading system and implications for management. Blood Adv. 2020;4(4):676-686.
20. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499-2513.
21. Rejeski K, Hansen DK, Bansal R, et al. The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma. J Hematol Oncol. 2023;16(1):88.
22. Rejeski K, Wang Y, Albanyan O, et al. The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene

autoleucel for relapsed or refractory MCL. Am J Hematol. 2023;98(11):1699-1710.

23. Rejeski K, Greco R, Onida F, et al. An International Survey on Grading, Diagnosis, and Management of Immune Effector Cell-Associated Hematotoxicity (ICAHT) Following CAR T-cell Therapy on Behalf of the EBMT and EHA. Hemasphere. 2023;7(5):e889.
24. Liang EC, Rejeski K, Fei T, et al. Development and validation of an automated computational approach to grade immune effector cell-associated hematotoxicity. Bone Marrow Transplant. 2024;59(7):910-917.
25. Rejeski K, Perez A, Iacoboni G, et al. Severe hematotoxicity after CD19 CAR-T therapy is associated with suppressive immune dysregulation and limited CAR-T expansion. Sci Adv. 2023;9(38):eadg3919.
26. Wudhikarn K, Palomba ML, Pennisi M, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J. 2020;10(8):79.
27. Rejeski K, Blumenberg V, Iacoboni G, et al. Identifying Early Infections in the Setting of CRS With Routine and Exploratory Serum Proteomics and the HT10 Score Following CD19 CAR-T for Relapsed/Refractory B-NHL. Hemasphere. 2023;7(4):e858.
28. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood. 2020;136(8):925-935.
29. Little JS, Aleissa MM, Beluch K, et al. Low incidence of invasive fungal disease following CD19 chimeric antigen receptor T-cell therapy for non-Hodgkin lymphoma. Blood Adv. 2022;6(16):4821-4830.
30. Haidar G, Dorritie K, Farah R, Bogdanovich T, Nguyen MH, Samanta P. Invasive Mold Infections After Chimeric Antigen Receptor-Modified T-Cell Therapy: A Case Series, Review of the Literature, and Implications for Prophylaxis. Clin Infect Dis. 2020;71(3):672-676.
31. Rejeski K, Kunz WG, Rudelius M, et al. Severe Candida glabrata pancolitis and fatal Aspergillus fumigatus pulmonary infection in the setting of bone marrow aplasia after CD19-directed CAR T-cell therapy - a case report. BMC Infect Dis. 2021;21(1):121.

32. Cheok KPL, Farrow A, Springell D, et al. Mucormycosis after CD19 chimeric antigen receptor T-cell therapy: results of a US Food and Drug Administration adverse events reporting system analysis and a review of the literature. Lancet Infect Dis. 2024;24(4):e256-e265.
33. Rejeski K, Wang Y, Hansen DK, et al. Applying the EHA/EBMT grading for ICAHT after CAR-T: comparative incidence and association with infections and mortality. Blood Adv. 2024;8(8):1857-1868.
34. Elsallab M, Ellithi M, Lunning MA, et al. Second primary malignancies after commercial CAR T-cell therapy: analysis of the FDA Adverse Events Reporting System. Blood. 2024;143(20):2099-2105.
35. Alkhateeb HB, Mohty R, Greipp P, et al. Therapy-related myeloid neoplasms following chimeric antigen receptor T-cell therapy for Non-Hodgkin Lymphoma. Blood Cancer J. 2022;12(7):113.
36. Xia Y, Zhang J, Li J, et al. Cytopenias following anti-CD19 chimeric antigen receptor (CAR) T cell therapy: a systematic analysis for contributing factors. Ann Med. 2022;54(1):2951-2965.
37. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant. 2019;54(10):1643-1650.
38. Jain MD, Jacobs MT, Gao F, et al. Bridging therapy with axicabtagene ciloleucel for large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. Blood Adv. 2024;8(4):1042-1050.
39. Roddie C, Neill L, Osborne W, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. Blood Adv. 2023;7(12):2872-2883.
40. Teipel R, Kroschinsky F, Kramer M, et al. Prevalence and variation of CHIP in patients with aggressive lymphomas undergoing CD19-directed CAR T-cell treatment. Blood Adv. 2022;6(6):1941-1946.
41. Miller PG, Sperling AS, Brea EJ, et al. Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. Blood Adv. 2021;5(15):2982-2986.
42. Zhao Y, Bai X, Guo S, et al. Efficacy and safety of CAR-T therapy targeting CLL1 in patients with extramedullary diseases of acute myeloid leukemia. J Transl Med. 2024;22(1):888.

43. Del Bufalo F, De Angelis B, Caruana I, et al. GD2-CART01 for Relapsed or Refractory High-Risk Neuroblastoma. N Engl J Med. 2023;388(14):1284-1295.
44. Hegde M, Navai S, DeRenzo C, et al. Autologous HER2-specific CAR T cells after lymphodepletion for advanced sarcoma: a phase 1 trial. Nat Cancer. 2024;5(6):880-894.
45. Saini NY, Swoboda DM, Greenbaum U, et al. Clonal Hematopoiesis Is Associated with Increased Risk of Severe Neurotoxicity in Axicabtagene Ciloleucel Therapy of Large B-Cell Lymphoma. Blood Cancer Discov. 2022;3(5):385-393.
46. Hamilton MP, Sworder B, Alig S, et al. CAR19 therapy drives expansion of clonal hematopoiesis and associated cytopenias. Transplant Cell Ther. 2024;30(2):S3-S4.
47. Nair MS, Silbert SK, Rejeski K, et al. Development of ALL-Hematotox (ALL-HT): Predicting post CAR T-cell hematotoxicity in B-cell acute lymphoblastic leukemia. Blood. 2024 Nov 19. [Epub ahead of print]
48. Faramand RG, Lee SB, Jain MD, et al. Baseline Serum Inflammatory Proteins Predict Poor CAR T Outcomes in Diffuse Large B-cell Lymphoma. Blood Cancer Discov. 2024;5(2):106-113.
49. Raj S, Xie J, Fei T, et al. An Inflammatory Biomarker Signature Reproducibly Predicts CAR-T Treatment Failure in Patients with Aggressive Lymphoma across the Zuma Trials Cohorts. Blood. 2023;142(Supplement 1):224.
50. Luft T, Benner A, Jodele S, et al. EASIX in patients with acute graft-versus-host disease: a retrospective cohort analysis. Lancet Haematol. 2017;4(9):e414-e423.
51. Greenbaum U, Strati P, Saliba RM, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021;5(14):2799-2806.
52. Pennisi M, Sanchez-Escamilla M, Flynn JR, et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. Blood Adv. 2021;5(17):3397-3406.
53. Frenking JH, Zhou X, Wagner V, et al. EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in

relapsed/refractory multiple myeloma. J Immunother Cancer. 2024;12(10):e009220.

54. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154.
55. Luo W, Li C, Zhang Y, et al. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis. BMC Cancer. 2022;22(1):98.
56. Kawalekar OU, RS OC, Fraietta JA, et al. Distinct Signaling of Coreceptors Regulates Specific Metabolism Pathways and Impacts Memory Development in CAR T Cells. Immunity. 2016;44(3):712.
57. Zhao Z, Condomines M, van der Stegen SJC, et al. Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells. Cancer Cell. 2015;28(4):415-428.
58. Juluri KR, Wu QV, Voutsinas J, et al. Severe cytokine release syndrome is associated with hematologic toxicity following CD19 CAR T-cell therapy. Blood Adv. 2022;6(7):2055-2068.
59. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv. 2020;4(15):3776-3787.
60. Wang Y, Song Z, Geng Y, et al. The risk factors and early predictive model of hematotoxicity after CD19 chimeric antigen receptor T cell therapy. Front Oncol. 2022;12:987965.
61. Frigault MJ, Graham CE, Berger TR, et al. Phase 1 study of CAR-37 T cells in patients with relapsed or refractory CD37+ lymphoid malignancies. Blood. 2024;144(11):1153-1167.
62. de Bruin AM, Demirel O, Hooibrink B, Brandts CH, Nolte MA. Interferon-gamma impairs proliferation of hematopoietic stem cells in mice. Blood. 2013;121(18):3578-3585.
63. Morales-Mantilla DE, King KY. The Role of Interferon-Gamma in Hematopoietic Stem Cell Development, Homeostasis, and Disease. Curr Stem Cell Rep. 2018;4(3):264-271.
64. Giudice V, Feng X, Lin Z, et al. Deep sequencing and flow cytometric characterization of expanded effector memory CD8(+)CD57(+) T cells

frequently reveals T-cell receptor Vbeta oligoclonality and CDR3 homology in acquired aplastic anemia. Haematologica. 2018;103(5):759-769.

65. Rejeski K, Wu Z, Blumenberg V, et al. Oligoclonal T-cell expansion in a patient with bone marrow failure after CD19 CAR-T therapy for Richter-transformed DLBCL. Blood. 2022;140(20):2175-2179.
66. Strati P, Li X, Deng Q, et al. Prolonged cytopenia following CD19 CAR T cell therapy is linked with bone marrow infiltration of clonally expanded IFNgamma-expressing CD8 T cells. Cell Rep Med. 2023;4(8):101158.
67. Penack O, Peczynski C, Koenecke C, et al. Severe cytopenia after CD19 CAR T-cell therapy: a retrospective study from the EBMT Transplant Complications Working Party. J Immunother Cancer. 2023;11(4):e006406.
68. Zhou J, Zhang Y, Shan M, et al. Cytopenia after chimeric antigen receptor T cell immunotherapy in relapsed or refractory lymphoma. Front Immunol. 2022;13:997589.
69. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. Blood Adv. 2020;4(13):3024-3033.
70. Logue JM, Peres LC, Hashmi H, et al. Early cytopenias and infections after standard of care idecabtagene vicleucel in relapsed or refractory multiple myeloma. Blood Adv. 2022;6(24):6109-6119.
71. Brudno JN, Natrakul D, Lam N, Dulau-Florea A, Yuan CM, Kochenderfer JN. Acute and delayed cytopenias following CAR T-cell therapy: an investigation of risk factors and mechanisms. Leuk Lymphoma. 2022;63(8):1849-1860.
72. Pascutti MF, Erkelens MN, Nolte MA. Impact of Viral Infections on Hematopoiesis: From Beneficial to Detrimental Effects on Bone Marrow Output. Front Immunol. 2016;7:364.
73. Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol. 2020;11:524.
74. Hines MR, Knight TE, McNerney KO, et al. Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome. Transplant Cell Ther. 2023;29(7):438.e1-438.e16.

75. Porter TJ, Lazarevic A, Ziggas JE, et al. Hyperinflammatory syndrome resembling haemophagocytic lymphohistiocytosis following axicabtagene ciloleucel and brexucabtagene autoleucel. Br J Haematol. 2022;199(5):720-727.
76. Rejeski K, Jain MD, Shah NN, Perales MA, Subklewe M. Immune effector cell-associated haematotoxicity after CAR T-cell therapy: from mechanism to management. Lancet Haematol. 2024;11(6):e459-e470.
77. Bhagwat AS, Torres L, Shestova O, et al. Cytokine-mediated CAR T therapy resistance in AML. Nat Med. 2024;30(12):3697-3708.
78. Ghilardi G, Paruzzo L, Patel V, et al. Efficacy and safety of bendamustine for lymphodepletion before lisocabtagene maraleucel. J Hematol Oncol. 2024;17(1):19.
79. Ghilardi G, Paruzzo L, Svoboda J, et al. Bendamustine lymphodepletion before axicabtagene ciloleucel is safe and associates with reduced inflammatory cytokines. Blood Adv. 2024;8(3):653-666.
80. Gagelmann N, Wulf GG, Duell J, et al. Hematopoietic stem cell boost for persistent neutropenia after CAR T-cell therapy: a GLA/DRST study. Blood Adv. 2023;7(4):555-559.
81. Ahmed N, Shahzad M, Shippey E, et al. Socioeconomic and Racial Disparity in Chimeric Antigen Receptor T Cell Therapy Access. Transplant Cell Ther. 2022;28(7):358-364.
82. Battram AM, Oliver-Caldes A, Suarez-Lledo M, et al. T cells isolated from G-CSF-treated multiple myeloma patients are suitable for the generation of BCMA-directed CAR-T cells. Mol Ther Methods Clin Dev. 2022;26:207-223.
83. Shahid Z, Jain T, Dioverti V, et al. Best Practice Considerations by The American Society of Transplant and Cellular Therapy: Infection Prevention and Management After Chimeric Antigen Receptor T Cell Therapy for Hematological Malignancies. Transplant Cell Ther. 2024;30(10):955-969.
84. Maung ZT, Wood AC, Jackson GH, Turner GE, Appleton AL, Hamilton PJ. Transfusion-associated graft-versus-host disease in fludarabine-treated B-chronic lymphocytic leukaemia. Br J Haematol. 1994;88(3):649-652.
85. Bindal P, Elavalakanar P, Trottier CA, et al. G-CSF Administration Is Associated with Worse Treatment Response and Survival after CAR T-Cell Therapy. Blood. 2022;140(Supplement 1):5238-5240.

86. Gaut D, Tang K, Sim MS, Duong T, Young P, Sasine J. Filgrastim associations with CAR T-cell therapy. Int J Cancer. 2021;148(5):1192-1196.
87. Miller KC, Johnson PC, Abramson JS, et al. Effect of granulocyte colony-stimulating factor on toxicities after CAR T cell therapy for lymphoma and myeloma. Blood Cancer J. 2022;12(10):146.
88. Ma S, Li H, Zhou D, et al. Associations of granulocyte colony-stimulating factor with toxicities and efficacy of chimeric antigen receptor T-cell therapy in relapsed or refractory multiple myeloma. Cytotherapy. 2023;25(6):653-658.
89. Li Y, Guo R, Wang L, Li S, Zhu Z, Tu P. G-CSF administration results in thrombocytopenia by inhibiting the differentiation of hematopoietic progenitors into megakaryocytes. Biochem Pharmacol. 2019;169:113624.
90. Shimba A, Ikuta K. Control of immunity by glucocorticoids in health and disease. Semin Immunopathol. 2020;42(6):669-680.
91. Wang J, Zhang M, Lyu H, et al. Low-dose administration of prednisone has a good effect on the treatment of prolonged hematologic toxicity post-CD19 CAR-T cell therapy. Front Immunol. 2023;14:1139559.
92. Nagle SJ, Murphree C, Raess PW, et al. Prolonged hematologic toxicity following treatment with chimeric antigen receptor T cells in patients with hematologic malignancies. Am J Hematol. 2021;96(4):455-461.
93. Beyar-Katz O, Perry C, On YB, et al. Thrombopoietin receptor agonist for treating bone marrow aplasia following anti-CD19 CAR-T cells-single-center experience. Ann Hematol. 2022;101(8):1769-1776.
94. Drillet G, Lhomme F, De Guibert S, Manson G, Houot R. Prolonged thrombocytopenia after CAR T-cell therapy: the role of thrombopoietin receptor agonists. Blood Adv. 2023;7(4):537-540.
95. Wesson W, Ahmed N, Rashid A, et al. Safety and efficacy of eltrombopag in patients with post-CAR T cytopenias. Eur J Haematol. 2024;112(4):538-546.
96. Beyar Katz O, Perry C, Grisariu-Greenzaid S, et al. Response rates of extra-nodal diffuse large B cell lymphoma to anti-CD19-CAR T cells: A real word retrospective multicenter study. Eur J Haematol. 2023;111(1):63-71.
97. Mingot-Castellano ME, Reguera-Ortega JL, Zafra Torres D, et al. Use of Eltrombopag to Improve Thrombocytopenia and Tranfusion Requirement in Anti-CD19 CAR-T Cell-Treated Patients. J Clin Med. 2024;13(17):5117.

98. Mullanfiroze K, Lazareva A, Chu J, et al. CD34+-selected stem cell boost can safely improve cytopenias following CAR T-cell therapy. Blood Adv. 2022;6(16):4715-4718.
99. Rejeski K, Burchert A, Iacoboni G, et al. Safety and feasibility of stem cell boost as a salvage therapy for severe hematotoxicity after CD19 CAR T-cell therapy. Blood Adv. 2022;6(16):4719-4725.
100. Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. Blood. 2024;143(16):1565-1575.
101. de Assis LH, Fassi DE, Hutchings M. Bispecific antibody therapies. Hematology Am Soc Hematol Educ Program. 2023;2023(1):216-222.
102. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23(8):1055-1065.
103. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol. 2023;41(12):2238-2247.
104. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231.
105. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell-Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial. J Clin Oncol. 2021;39(18):1959-1970.
106. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med. 2022;387(24):2232-2244.
107. D'Souza A, Shah N, Rodriguez C, et al. A Phase I First-in-Human Study of ABBV-383, a B-Cell Maturation Antigen x CD3 Bispecific T-Cell Redirecting Antibody, in Patients With Relapsed/Refractory Multiple Myeloma. J Clin Oncol. 2022;40(31):3576-3586.

108. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022;387(6):495-505.
109. Usmani SZ, Garfall AL, van de Donk N, et al. Teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665-674.
110. Lievin R, Di Blasi R, Morin F, et al. Effect of early granulocyte-colony-stimulating factor administration in the prevention of febrile neutropenia and impact on toxicity and efficacy of anti-CD19 CAR-T in patients with relapsed/refractory B-cell lymphoma. Bone Marrow Transplant. 2022;57(3):431-439.
111. Galli E, Allain V, Di Blasi R, et al. G-CSF does not worsen toxicities and efficacy of CAR-T cells in refractory/relapsed B-cell lymphoma. Bone Marrow Transplant. 2020;55(12):2347-2349.
112. Barreto JN, Bansal R, Hathcock MA, et al. The impact of granulocyte colony stimulating factor on patients receiving chimeric antigen receptor T-cell therapy. Am J Hematol. 2021;96(10):E399-E402.
113. Sureda A, Kröger N, Apperley J, Gratwohl A. The EBMT: History, Present, and Future. In: Sureda A, Corbacioglu S, Greco R, Kröger N, Carreras E. (eds) The EBMT Handbook. Springer, Cham. Available at https://doi.org/10.1007/978-3-031-44080-9_2. Last accessed in October, 2024.
114. Carson JL, Stanworth SJ, Guyatt G, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. JAMA. 2023;330(19):1892-1902.
115. Schiffer CA, Bohlke K, Delaney M, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(3):283-299.
116. Davis JA, Sborov DW, Wesson W, et al. Efficacy and Safety of CD34+ Stem Cell Boost for Delayed Hematopoietic Recovery After BCMA Directed CAR T-cell Therapy. Transplant Cell Ther. 2023;29(9):567-571.
117. Mohan M, Szabo A, Patwari A, et al. Autologous stem cell boost improves persistent immune effector cell associated hematotoxicity following BCMA directed chimeric antigen receptor T (CAR T) cell therapy in multiple myeloma. Bone Marrow Transplant. 2024;59(5):647-652.

118. Baur R, Jitschin R, Kharboutli S, et al. Thrombopoietin receptor agonists for acquired thrombocytopenia following anti-CD19 CAR-T-cell therapy: a case report. J Immunother Cancer. 2021;9(7):e002721.
119. Laham Y, Ringelstein-Harlev S, Kurnik D, et al. High-dose intravenous immunoglobulin may be an efficient treatment option for patients with late-onset high-grade immune effector cell-associated hematotoxicity refractory to standard therapies. Haematologica. 2025 Jan 9. [Epub ahead of print]
120. Xing L, Wang Y, Liu H, et al. Case Report: Sirolimus Alleviates Persistent Cytopenia After CD19 CAR-T-Cell Therapy. Front Oncol. 2021;11:798352.

Table 1: Hematotoxicity Grading Systems[20] and Definitions of Recovery Phenotypes

Grading System	Cytopenia	Grade 1	Grade 2	Grade 3	Grade 4
CTACE	**Neutropenia**	ANC <LLN 1500/µL	ANC <1500-1000/µL	ANC <1000-500/µL	ANC <500/µL
	Anemia	Hgb <LLN 10 g/dL	Hgb <10.0-8.0 g/dL	Hgb <8.0 g/dL; transfusion	Life-threatening intervention
	Thrombo-cytopenia	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	Never above ANC 500/µL
				ANC <100/µL* for ≥7 days**	ANC <100/µL for ≥14 days
	Late (after day +30)* **	ANC <1500/µL	ANC <1000/µL	ANC <500/µL	ANC <100/µL
Phenotypes of Neutrophil Recovery	▪ **Quick Recovery:** sustained neutrophil recovery without a second dip below an ANC <1000/µL. ▪ **Intermittent Recovery:** neutrophil recovery (ANC >1500/µL) followed by a second dip below an ANC <1000/µL. ▪ **Aplastic Recovery:** continuous severe neutropenia (ANC <500/µL) for ≥14 days.				

*profound neutropenia (ANC <100/µL), **protracted neutropenia (≥7 days).

***Non-transient neutropenia, see additional definitions from Liang et al. clarifying the necessary second measurement of ANC <1500/µL within a certain time period.

Abbreviations: ANC: absolute neutrophil count; Hgb: hemoglobin; LLN: lower limit of normal; CTACE: Common Terminology Criteria for Adverse Events; ICAHT: Immune Effector Cell-Associated Hematotoxicity

Table 2: Risk factors associated with an increased risk of post-CAR-T cytopenias

	Risk Factors	Additional Comments	References
Treatment-related features	Number of prior therapy lines Prior hematopoietic stem cell transplantation Administration of bridging therapies	Impact hematopoietic function and bone marrow reserve prior to CAR-T	Xia et al.[36] Penack et al.[67] Fried et al.[37] Zhou et al.[68] 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 > IL	Xia et al.[36] Rejeski et al.[33]
	Disease burden at time of CAR-T 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 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 overlapping symptom	Sandler et al.[73] Hines et al.[74] Porter et al.[75]

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

Table 3: Supportive and therapeutic management of ICAHT

Intervention	Practical considerations	Recommendations	Disease	References
G-CSF	Day+2 or +5 following CAR-T	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 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 cells 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) *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:*		Sureda et al.[113] Carson et al.[114] Schiffer et al.[115]

		▪ Patients with platelet counts ≤10 × 10^9/L ▪ Patients with active bleed, febrile, or active infections: platelet counts ≤20 × 10^9/L		
Stem cell boost	Autologous stem cells - mostly unavailable in lymphoma patients Allogeneic SCT - most patients are not appropriate candidates	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]
	Alternative treatment strategies with lower levels of evidence			
TPO mimetics	Not to take together with dairy products	Initiate in cases of prolonged thrombocytopenia requiring repeated platelet transfusions, i.e., 2 or more units of platelet infusion 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]

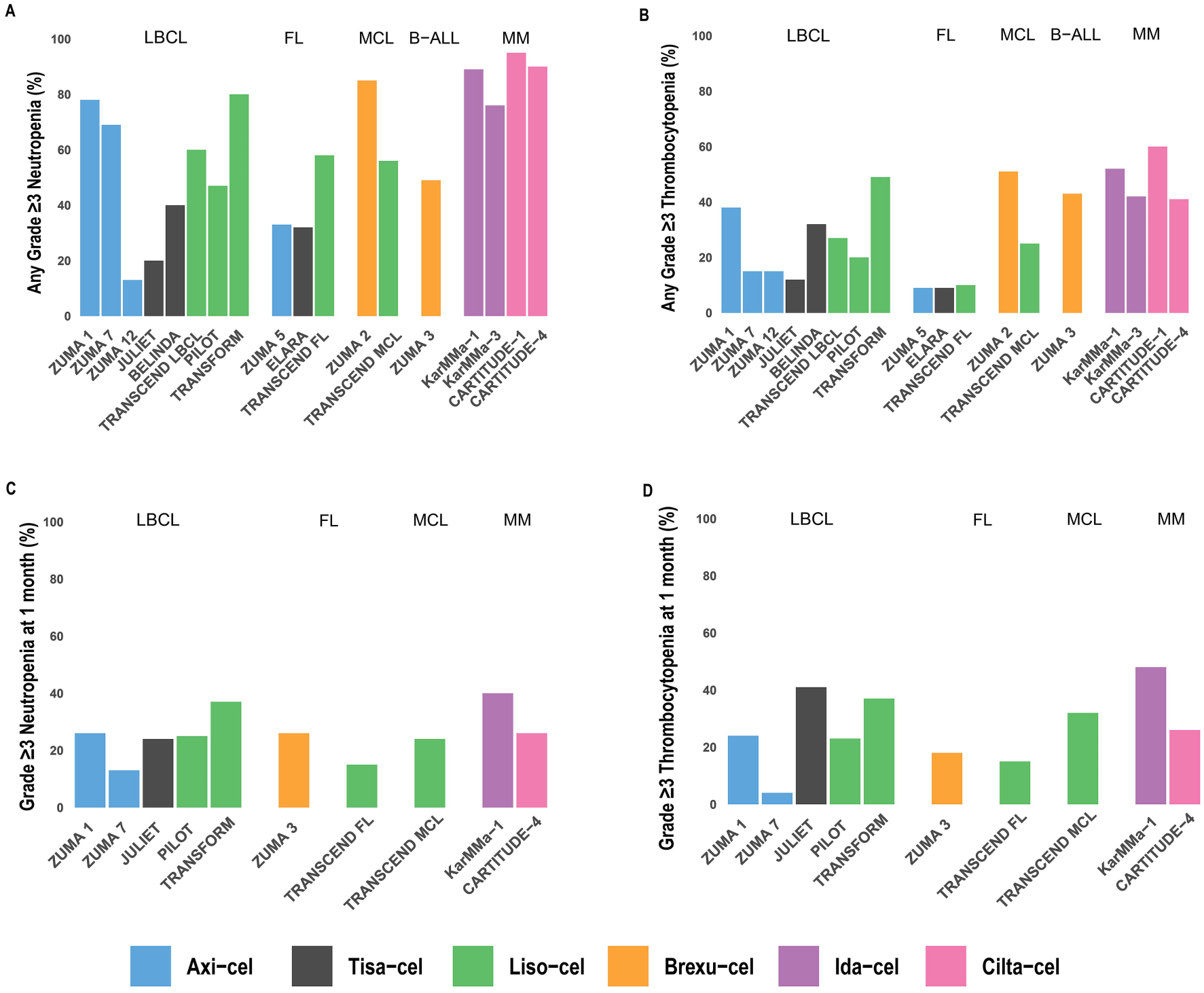
SCT: stem cell transplantation; TPO: thrombopoietin; B-ALL: B-cell acute lymphoblastic leukemia; MM: multiple myeloma, Intravenous immunoglobulin

Figure legends:

Figure 1. Grade ≥ 3 Neutropenia and Thrombocytopenia in the Pivotal CAR T-Cell Therapy Studies

LBCL - large B-cell lymphoma, FL - follicular lymphoma*, MCL - mantle cell lymphoma, B-ALL - B cell acute lymphoblastic leukemia, MM - multiple myeloma, * ZUMA 5 included follicular and marginal zone lymphoma

Figure 2. Clinical implications of ICAHT after CAR-T


A
Any Grade ≥3 Neutropenia (%)
LBCL
FL
MCL
B−ALL
MM
ZUMA 1
ZUMA 7
ZUMA 12
JULIET
BELINDA
TRANSCEND LBCL
PILOT
TRANSFORM
ZUMA 5
ELARA
TRANSCEND FL
ZUMA 2
TRANSCEND MCL
ZUMA 3
KarMMa−1
KarMMa−3
CARTITUDE−1
CARTITUDE−4
B
Any Grade ≥3 Thrombocytopenia (%)
C
Grade ≥3 Neutropenia at 1 month (%)
D
Grade ≥3 Thrombocytopenia at 1 month (%)
Axi−cel
Tisa−cel
Liso−cel
Brexu−cel
Ida−cel
Cilta−cel

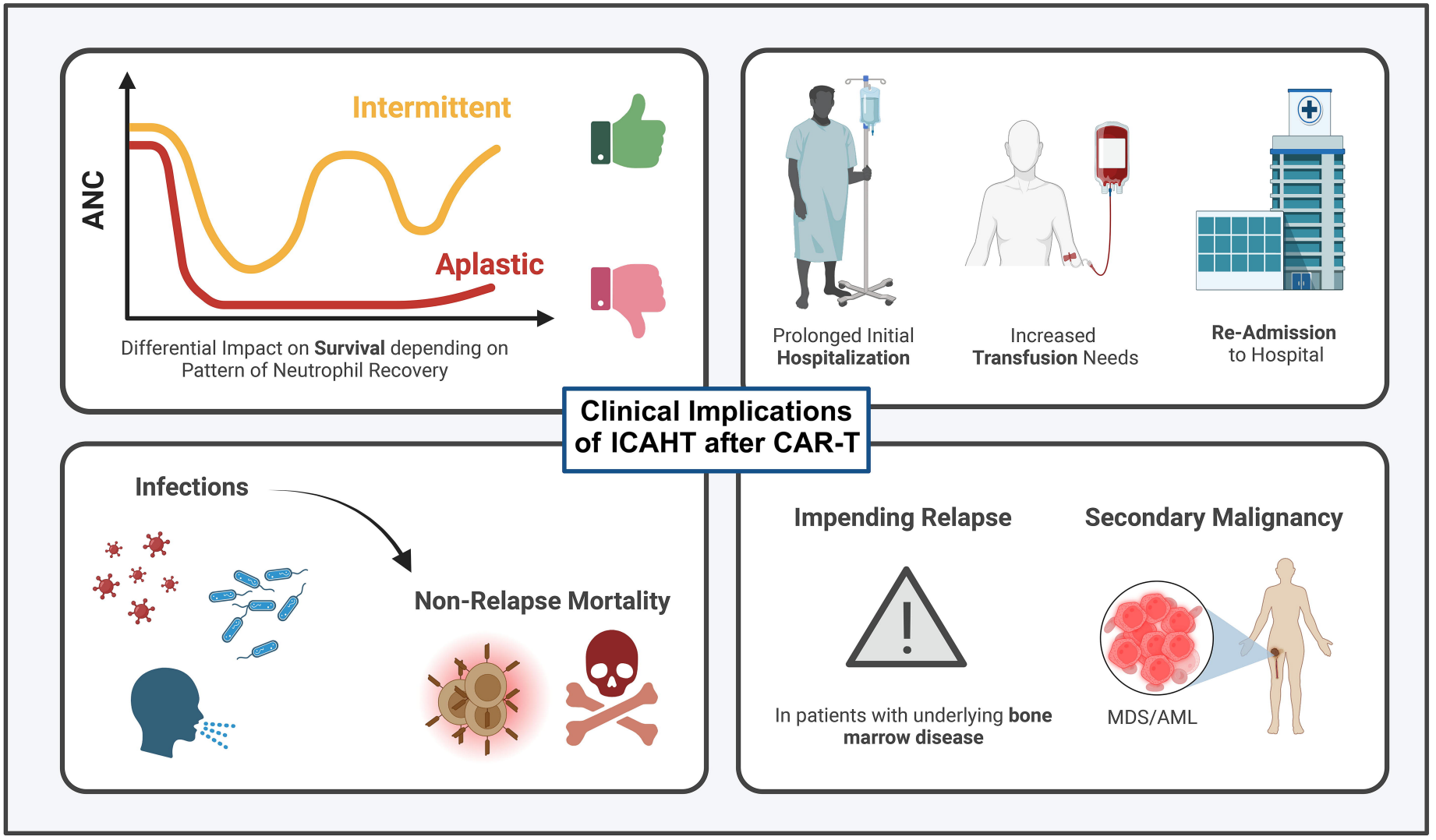

Intermittent
ANC
Aplastic
Differential Impact on Survival depending on Pattern of Neutrophil Recovery
Prolonged Initial Hospitalization
Increased Transfusion Needs
Re-Admission to Hospital
Clinical Implications of ICAHT after CAR-T
Infections
Non-Relapse Mortality
Impending Relapse
In patients with underlying bone marrow disease
Secondary Malignancy
MDS/AML

Table S1. Cytopenia Rates in the Pivotal CAR T-cell Therapy Studies

Study	Disease	Product	Number of patients	CRS grade ≥3	Any grade ≥3 neutropenia	Any grade ≥3 thrombocytopenia	Any grade ≥3 anemia	Grade ≥3 neutropenia present 1 month	Grade ≥3 thrombocytopenia present 1 month
ZUMA-1[1,2]	LBCL	Axi-cel	108	13%	78%	38%	43%	26%	24%
ZUMA-7[3,4]	LBCL	Axi-cel	170	6%	69%	15%	30%	13%	4%
ZUMA-12[5]	LBCL	Axi-cel	40	8%	13%	15%	30%	N/A	N/A
JULIET[6]	LBCL	Tisa-cel	11	22	20%	12%	39%	24%	41%
BELINDA[7]	LBCL	Tisa-cel	155	5%	40%	32%	33%	N/A	N/A
TRANSCEND LBCL[8]	LBCL	Liso-cel	269	42%	60%	27%	37%	N/A	N/A
PILOT[9]	LBCL	Liso-cel	61	1%	47%	20%	11%	25%	23%
TRANSFORM[10]	LBCL	Liso-cel	90	1%	80%	49%	49%	37%	37%
ZUMA-5[11]	FL & MZL	Axi-cel	148	7%	33%	9%	25%	N/A	N/A
ELARA Tisa-cel[12]	FL	Tisa-cel	97	49%	32%	9%	13%	N/A	N/A
TRANSCEND FL[13]	FL	Liso-cel	130	1%	58%	10%	10%	15%	15%

ZUMA-2[14]	MCL	Brex-cel	68	15%	85%	51%	50%	N/A	N/A
TRANSCEND MCL[15]	MCL	Liso-cel	88	1%	56%	25%	38%	24%	32%
ZUMA-3[16]	B-ALL	Brex-cel	55	24%	49%	43%	49%	26%	18%
KarMMa-1[17]	MM	Ide-cel	128	5%	89%	52%	60%	40%	48%
KarMMa-3[18]	MM	Ide-cel	225	5%	76%	42%	51%	N/A	N/A
CARTITUDE-1[19]	MM	Cilta-cel	97	4%	95%	60%	68%	N/A	N/A
CARTITUDE-4[20]	MM	Cilta-cel	176	1%	90%	41%	36^	26%	26%

LBCL: Large B-cell Lymphoma, Axi-cel: Axicabtagene Ciloleucel, Tisa-cel: Tisagenlecleucel, Liso-cel: Lisocabtagene Maraleucel, Brex-cel: Brexucabtagene Autoleucel, FL: Follicular Lymphoma, MZL: Marginal Zone Lymphoma, MCL: Mantle Cell Lymphoma, B-ALL: B-cell Acute Lymphoblastic Leukemia, MM: Multiple Myeloma, CRS: Cytokine Release Syndrome, N/A: Not Available

Table S2. Key Studies Analyzing Stem Cell Boost Administration

References	Single /multi center	CAR-T product	Disease	Patient number	Cell source	Number of infused cells/kg (median)	Time from CAR-T to stem cell infusion (median), days	Duration of neutropenia before cell boost, days	Response / engraftment	Median time to response, days (range)	Toxicity
Gagelmann et al[21]	Multi	Axi-cel: 20 Tisa-cel: 7 allo CAR-T cells: 3 Brex-cel: 1	LBCL B-ALL MCL	31	Auto: 30 Allo: 1	3.6×10^6 (1.1-11.5)	43	38 (7-151)	Neut: 26/31 (84%)	9 (7-14)	No
Mullanfiroze et al[22]	Single	CAR-T cells investigational: 6 Tisa-cel: 1	B-ALL	7	Allo	6.75×10^6 (2.5-11.2)	79 (57-502)	Not reported	Neut: 4/5 evaluable	Neut: 42 (11-192) Plt: 33 (7-73)	No aGVHD or cGVHD Grade 2 CRS 10 days after SCB
Rejeski et al[23]	Multi	Axi-cel: 9 Tisa-cel: 2 Brex-cel: 1	LBCL B-ALL MCL	12	Auto: 9 Allo: 3	3.1×10^6 (1.7-7.5)	69 (35-617)	42	Neut: 11/11 (100%) Plt: 7/9 (78%)	Neut:15 (6-124) Plt: 21 (12-34)	No GVHD
Davis et al[24]	Multi	BCMA directed CAR-T	RRMM	19	Auto	2.75×10^6 (1.76-7.38)	53 (24-126)	Not reported	18/19 (95%) patients successfully recovered hematopoiesis	Neut: 14 (9-39) Plt: 17 (12-39) Hgb: 23 (6-34)	No infusion reactions
Mohan et al[25]	Multi	BCMA directed CAR-T (ide-cel) or (cilta-cel) or investigational	RRMM	16	Auto	3.84×10^6 (1.05–9.04)	116 (29–270)	Not reported	Neut: 16/16 (100%)	Not reported	No side effects reported

Axi-cel: Axicabtagene Ciloleucel, Tisa-cel: Tisagenlecleucel, Liso-cel: Lisocabtagene Maraleucel, Brex-cel: Brexucabtagene Autoleucel, BCMA: B-cell Maturation Antigen, Ide-cel: Idecabtagene Vicleucel, Cilta-cel: Ciltacabtagene Autoleucel, LBCL: Large B-cell Lymphoma, B-ALL: B-cell Acute Lymphoblastic Leukemia, MCL: Mantle Cell Lymphoma, RRMM: Relapse/Refractory Multiple Myeloma, Auto: Autologous, Allo: Allogeneic, aGVHD: Acute Graft-Versus-Host Disease, cGVHD: Chronic Graft-Versus-Host Disease, CRS: Cytokine Release Syndrome, SCB: Stem Cell Boost, Neut: Neutrophils, Plt: Platelet, Hgb: Hemoglobin

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
2. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* 2019;20(1):31-42.
3. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med.* 2022;386(7):640-654.
4. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *N Engl J Med.* 2023;389(2):148-157.
5. Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. *Nat Med.* 2022;28(4):735-742.
6. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2019;380(1):45-56.
7. Bishop MR, Dickinson M, Purtill D, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. *N Engl J Med.* 2022;386(7):629-639.
8. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet.* 2020;396(10254):839-852.
9. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. *Lancet Oncol.* 2022;23(8):1066-1077.

10. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet.* 2022;399(10343):2294-2308.
11. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. *Lancet Oncol.* 2022;23(1):91-103.
12. Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med.* 2022;28(2):325-332.
13. Morschhauser F, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. *Nat Med.* 2024;30(8):2199-2207.
14. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med.* 2020;382(14):1331-1342.
15. Wang M, Siddiqi T, Gordon LI, et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. *J Clin Oncol.* 2024;42(10):1146-1157.
16. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet.* 2021;398(10299):491-502.
17. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2021;384(8):705-716.
18. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma. *N Engl J Med.* 2023;388(11):1002-1014.
19. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet.* 2021;398(10297):314-324.

20. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med.* 2023;389(4):335-347.
21. Gagelmann N, Wulf GG, Duell J, et al. Hematopoietic stem cell boost for persistent neutropenia after CAR T-cell therapy: a GLA/DRST study. *Blood Adv.* 2023;7(4):555-559.
22. Mullanfiroze K, Lazareva A, Chu J, et al. CD34+-selected stem cell boost can safely improve cytopenias following CAR T-cell therapy. *Blood Adv.* 2022;6(16):4715-4718.
23. Rejeski K, Burchert A, Iacoboni G, et al. Safety and feasibility of stem cell boost as a salvage therapy for severe hematotoxicity after CD19 CAR T-cell therapy. *Blood Adv.* 2022;6(16):4719-4725.
24. Davis JA, Sborov DW, Wesson W, et al. Efficacy and Safety of CD34+ Stem Cell Boost for Delayed Hematopoietic Recovery After BCMA Directed CAR T-cell Therapy. *Transplant Cell Ther.* 2023;29(9):567-571.
25. Mohan M, Szabo A, Patwari A, et al. Autologous stem cell boost improves persistent immune effector cell associated hematotoxicity following BCMA directed chimeric antigen receptor T (CAR T) cell therapy in multiple myeloma. *Bone Marrow Transplant.* 2024;59(5):647-652.