Immune effector cell-associated haematotoxicity after CAR T-cell therapy: from mechanism to management

Kai Rejeski, Michael D Jain, Nirali N Shah, Miguel-Angel Perales, Marion Subklewe

Genetically engineered chimeric antigen receptor (CAR) T cells have become an effective treatment option for several advanced B-cell malignancies. Haematological side-effects, classified in 2023 as immune effector cell-associated haematotoxicity (ICAHT), are very common and can predispose for clinically relevant infections. As haematopoietic reconstitution after CAR T-cell therapy differs from chemotherapy-associated myelosuppression, a novel classification system for early and late ICAHT has been introduced. Furthermore, a risk stratification score named CAR-HEMATOTOX has been developed to identify candidates at high risk of ICAHT, thereby enabling risk-based interventional strategies. Therapeutically, growth factor support with granulocyte colony-stimulating factor (G-CSF) is the mainstay of treatment, with haematopoietic stem cell (HSC) boosts available for patients who are refractory to G-CSF (if available). Although the underlying pathophysiology remains poorly understood, translational studies from the past 3 years suggest that CAR T-cell-induced inflammation and baseline haematopoietic function are key contributors to prolonged cytopenia. In this Review, we provide an overview of the spectrum of haematological toxicities after CAR T-cell therapy and offer perspectives on future translational and clinical developments.

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Adult BMT and Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA (K Rejeski MD, M-A Perales MD); **Department of Medicine III, LMU University Hospital, LMU Munich, Munich, Germany** (K Rejeski, Prof M Subklewe MD); **Laboratory for Translational Cancer Immunology, LMU Gene Center, Munich, Germany** (K Rejeski, Prof M Subklewe); **Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL, USA** (M D Jain MD); **Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA** (N N Shah MD)

Correspondence to: Kai Rejeski, Adult BMT and Cellular Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA **rejeskik@mskcc.org**

and

Prof Marion Subklewe, Laboratory for Translational Cancer Immunology, LMU Gene Center, Munich 81377, Germany **marion.subklewe@med.uni-muenchen.de**

Introduction

Cellular immunotherapies with genetically engineered chimeric antigen receptor (CAR) T cells that target B-cell antigens, such as CD19 or BCMA, have rapidly altered the treatment landscape of several lymphoid malignancies. These therapies have led to the approval of six CAR T-cell products by the US Food and Drug Administration (FDA) across a spectrum of haematological disease indications, with many more in the developmental pipeline. Furthermore, CAR T-cell platforms are being actively explored for the treatment of several solid tumours and autoimmune diseases.[1,2] The profound systemic immune response elicited by CAR T cells upon target antigen recognition and subsequent expansion can result in a unique toxicity profile. Although much attention has been paid to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) as prototypical side-effects with distinct management protocols,[3] immune effector cell-associated haematotoxicity (ICAHT) is the most common CAR T-cell-related adverse event across clinical trials and the real-world setting.[4–6] Haematotoxicity is also observed irrespective of the applied CAR T-cell product, target antigen, and disease entity.[7]

Although it is tempting to attribute haematotoxicity as only a consequence of the myelotoxic lymphodepleting chemotherapy applied before CAR T-cell infusion (mainly fludarabine and cyclophosphamide), cytopenias are often long lasting and delayed in nature—occurring long after the application of CAR T cells. Cytopenias are typically characterised by an archetypal biphasic temporal course with intermittent recovery followed by a second decline in absolute neutrophil counts (ANC).[8,9] In a smaller proportion of patients, severe cases of bone marrow aplasia have been described (the aplastic phenotype).[9–12] In addition, prolonged cytopenias have been described to last from months to several years after CAR T-cell infusion.[13] Together, these clinical observations strongly suggest a CAR T-cell-induced mechanism of myelosuppression, although the underlying pathophysiology remains incompletely understood.

The clinical relevance of haematotoxicity lies in the haemorrhagic diathesis and increased risk of infectious complications. Both neutropenia and lymphopenia predispose for bacterial, fungal, and viral infections.[14] Risk of infection is further compounded by B-cell aplasia and hypogammaglobulinemia as expected on target off-tumor toxicities of B cell-targeting CAR T-cell therapies. As a result, life-threatening infectious complications drive non-relapse mortality after CAR T-cell therapy across diverse treatment settings.[15] Moreover, transfusion dependency substantially contributes to therapy-related morbidity, prolonging hospital stays and increasing the use of health-care resources.[16] Overall, there remains marked heterogeneity in the reporting of cytopenias and concerning standard diagnostic examination and management.[17] Therefore, efforts in 2023 by the European Hematology Association (EHA) and the European Society of Bone Marrow Transplantation (EBMT) resulted in the classification of ICAHT as a distinct toxicity category of cell therapy with its own consensus grading framework and severity-based treatment recommendations.[7,17]

In this Review, we share perspectives on the range of encountered haematological side-effects of CAR T-cell therapy. Specifically, we provide an overview on the expected incidence rates of early and late ICAHT across a range of lymphoid malignancies and plasma cell dyscrasias. We shed light on the classification systems used to date and outline their potential advantages and pitfalls. Next, we describe what is known about clinical risk factors and potential pathomechanisms, focusing on mechanistic differences on the basis of the different patterns of neutrophil recovery after CAR T-cell infusion. Finally, we discuss the evidence base for therapeutic options, such as granulocyte colony-stimulating factor (G-CSF), thrombopoietin receptor agonists, and haematopoietic stem cell (HSC) boosts. Our overarching

goal is to inform CAR T-cell practitioners on ICAHT as a clinically relevant side-effect of cell therapy, to put forth a framework for future translational efforts, and to provide suggestions to improve management of cytopenias in patients with haematological malignancies.

Haematological complications of CAR T-cell therapy

When approaching haematological side-effects of CAR T-cell therapies, one can broadly separate three distinct phases: before CAR T-cell infusion, early ICAHT (days 0–30), and late ICAHT (after day 30; figure 1). The pretherapeutic phase is characterised by the unique patient history, the number of previous cytotoxic treatment lines given, and the commonly applied holding or bridging therapies immediately preceding CAR T-cell infusion.[18,19] For example, chemotherapy-based bridging can result in baseline cytopenias, which can reflect an impaired haematopoietic reserve.[20] Other relevant baseline risk factors of haematotoxicity are the degree of systemic inflammation (eg, elevations of serum C-reactive protein or ferritin) and the presence of underlying bone marrow infiltration. To risk-stratify patients for developing cytopenias and associated infections before lymphodepletion, the CAR-HEMATOTOX score was established in a multicentre cohort of patients with large B-cell lymphoma and was then validated for patients with mantle cell lymphoma and multiple myeloma.[9–11,21,22] The score also appears to be useful for identifying patients at high risk of disease progression and prolonged hospitalisation.

The applied lymphodepleting chemotherapy (typically fludarabine [range 25–30 mg/m²] and cyclophosphamide [range 250–500 mg/m²]) facilitates an expected early nadir phase that can extend until 10 days after CAR T-cell infusion. During this early phase, a delay in count recovery can be aggravated by high-grade CRS and associated cytokine patterns, especially elevated concentrations of IL-6 and IFN-γ.[23,24] Three typical trajectories of early neutrophil recovery have emerged. First, quick recovery refers to transient and self-resolving cytopenia due to the applied lymphodepleting chemotherapy. Second, intermittent recovery describes the commonly observed biphasic pattern with count recovery, followed by a second or multiple dips. Third, the clinically challenging aplastic phenotype is characterised by marked bone marrow

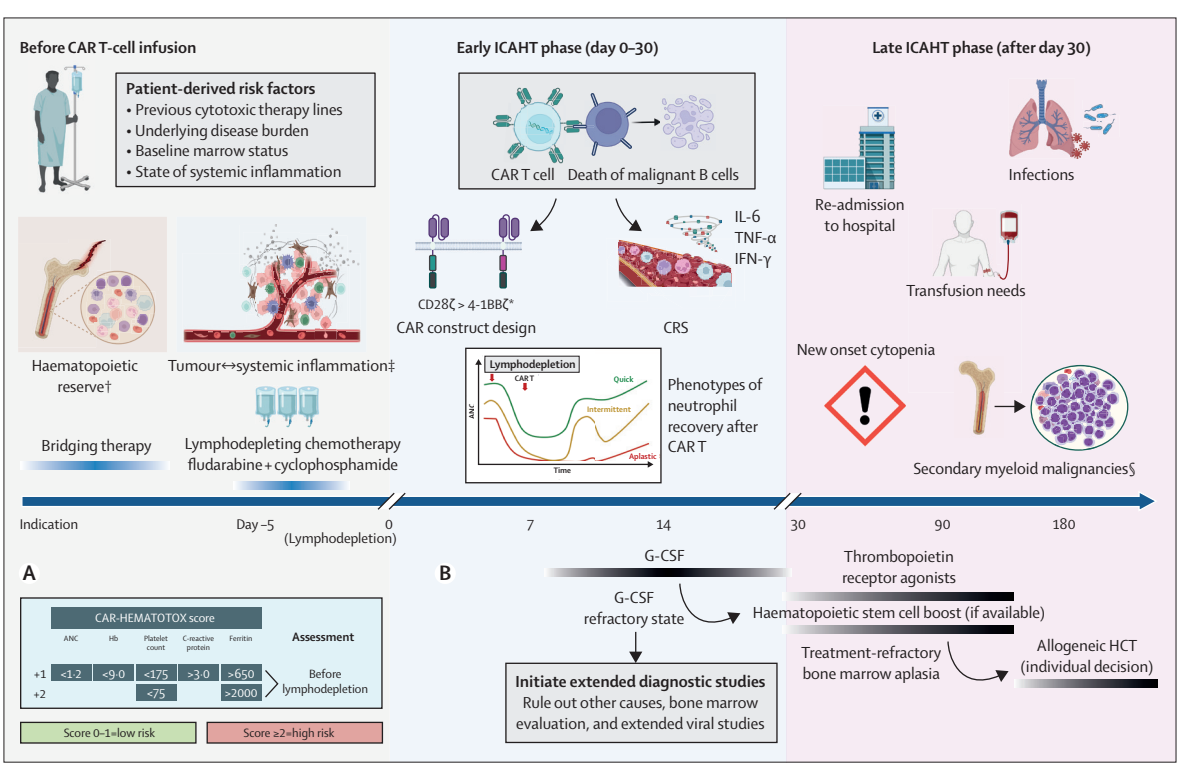

Figure 1: **Timeline of haematological toxicities of CAR T-cell therapy**
Overview of the most important risk factors, clinical considerations, and complications of haematotoxicity across the three phases in relation to CAR T-cell infusion. (A) Individualised risk assessment with the CAR-HEMATOTOX score, which is assessed before lymphodepletion (day -5) and separates patients into low (score 0–1) versus high (score ≥2) risk for severe haematotoxicity. (B) Summary of management strategies to treat cytopenias after CAR T-cell therapy. ANC=absolute neutrophil count. CAR=chimeric antigen receptor. CRP=C-reactive protein. CRS=cytokine release syndrome. Hb=haemoglobin. HCT=haematopoietic cell transplantation. ICAHT=immune effector cell-associated haematotoxicity. G-CSF=granulocyte colony-stimulating factor. *Patients receiving the CD28ξ endodomain CAR T-cell therapy had higher haematotoxicity than those receiving the 4-1BBξ endodomain therapy. †Measured by Hb concentration, ANC, and platelet count. ‡Measured by concentrations of lactate dehydrogenase, C-reactive protein, and ferritin, and the total metabolic tumour volume. §Myelodysplastic syndromes and acute myeloid leukaemia.

	Fried et al (2019)[8]	Jain et al (2020)[26]	Logue et al. (2021)[6]	Rejeski et al (2021)[9]	Juluri et al (2022)[23]	Penack et al (2023)[27]	Rejeski et al (2023a)[11]	Rejeski et al (2023b)[10]
Number of patients in study	35	83	85	258	173	398	113	103
Median age (range)	27 (3·5–55)	58 (19–85)	64 (28–79)	63 (19–83)	55 (20–76)	61 (18–81)	65 (39–81)	66 (49–89)
Haematological malignancy	Acute lymphocytic leukaemia (19); B cell non-Hodgkin lymphoma (16)	Large B-cell lymphoma (40); acute lymphocytic leukaemia (37); multiple myeloma (6)	Large B-cell lymphoma	Large B-cell lymphoma	Acute lymphocytic leukaemia (62); chronic lymphocytic leukaemia (48); B-cell non-Hodgkin lymphoma (63)	Large B-cell lymphoma	Multiple myeloma	Mantle cell lymphoma
Median number of previous lines of chemotherapy (range)	..	4 (1–9)	3 (1–8)	3 (2–11)	4 (1–11)	3 (1–8)	6 (5–6†)	3 (2–4‡)
Previous autologous HCT	37%*	18%	25%	27%	13%	24%	88%	32%
Previous allogeneic HCT	..	19%	2·4%	..	20%	3·6%	3·5%	3%
Underlying bone marrow involvement	..	..	..	14%	..	..	46%	37%
Median serum lactate dehydrogenase concentration before CAR T-cell therapy (95% CI)	..	..	..	276 (260–302)	..	..	217 (202–242)	208 (19 4–218)
Median platelet count before CAR T-cell therapy (95% CI), G/L	..	..	..	164 (152–178)	123 (64–196‡)	..	144 (125–158)	164 (152–178)
Median serum ferritin concentration before CAR T-cell therapy (95% CI), ng/mL	..	..	..	501 (378–647)	..	..	211 (120–354)	243 (184–282)
Applied CAR product	Local product	Axicabtagene ciloleucel (30); tisagenlecleucel (10); local product (43)	Axicabtagene ciloleucel	Axicabtagene ciloleucel (170); tisagenlecleucel (88)	Local product (CD28ξ + 4-1BBξ)	Axicabtagene ciloleucel (245); tisagenlecleucel (153)	Idecabtagene vicleucel (106); ciltacabtagene autoleucel (7)	Brexucabtagene autoleucel
Target antigen	CD19	CD19 and BCMA	CD19	CD19	CD19	CD19	BCMA	CD19
Grade ≥3 CRS	14%	23%	9%	11%	15%	NR	5%	6%
Thrombocytopenia grade ≥3	28%	65%	NR	62%	44%	Any grade 3 or 4 cytopenia 100%	50%	57%
Anaemia grade ≥3	55%	77%	NR	69%	16%	Any grade 3 or 4 cytopenia 100%	50%	51%
Neutropenia grade ≥3	72%	95%	NR	91%	59%	Any grade 3 or 4 cytopenia 100%	73%	88%
Prolonged neutropenia in days after CAR T-cell infusion	Day +42 62%	Day +30 67%; day +90 20%	Day +30 30%; day +90 12·5%	Day +21 64%	Day +28 46%	Cytopenia at day +30 9%; cytopenia at day +90 12%	Day +21 50%	Day +28 47%
Prolonged thrombocytopenia in days after CAR T-cell infusion	Day +42 44%	Day +30 49%; day +90 10%	Day +30 26%; day +90 5·4%	NR	Day +28 34%	Cytopenia at day +30 9%; cytopenia at day +90 12%	Days 31–100 28%	Days 31–100 35%
Phenotypes of neutrophil recovery	..	..	..	Quick 25%; intermittent 52%; aplastic 23%	..	..	Quick 40%; intermittent 44%; aplastic 16%	Quick 41%; intermittent 38%; aplastic 21%

(Table 1 continues on next page)

	Fried et al (2019)[8]	Jain et al (2020)[26]	Logue et al. (2021)[6]	Rejeski et al (2021)[9]	Juluri et al (2022)[23]	Penack et al (2023)[27]	Rejeski et al (2023a)[11]	Rejeski et al (2023b)[10]
(Continued from previous page)								
Median follow-up time after CAR T-cell therapy	NR	6 months	12·8 months	NR	40·8 months	NR	7·9 months	15·4 months
Association with infectious events	NR	NR	Infections linked to high-grade CRS or ICANS and steroid use; association with neutropenia duration was not studied	NR	NR	Infections reported both in the patients with and without severe cytopenias	Increased infection rate in patients with severe haematotoxicity, particularly bacterial infections	Increased infection rate in patients with severe haematotoxicity, particularly bacterial infections
Additional comments	Biphasic pattern of cytopenia; late cytopenia linked to high-grade CRS, before HSCT and SDF-1 alterations	Association between high-grade CRS or ICANS and markers of acute inflammation with delayed count recovery	Study also explores long-term immune reconstitution patterns following axicabtagene ciloleucel	Development of CAR-HEMATOTOX score with independent validation; high scores associated with adverse treatment outcomes	Association of haematotoxicity with high-grade CRS and CRS-related inflammatory patterns (especially increased serum IL-6 concentrations)	Severe cytopenia linked to the number of previous treatment lines; reduced progression-free survival in patients with severe haematotoxicity	Validation of CAR-HEMATOTOX score, including for infections, non-relapse mortality, and survival	Validation of CAR-HEMATOTOX score, including for infections, non-relapse mortality, and survival

Data are depicted as n (%) unless otherwise specified. +=number of days after CAR T-cell infusion. CAR=chimeric antigen receptor. CRS=cytokine release syndrome. HCT=haematopoietic cell transplantation. ICANS=immune effector cell-associated neurotoxicity syndrome. NR=not reported. *Reference did not specify autologus or allogeneic transplantation. †95% CI. ‡IQR.

Table 1: **Overview of studies examining haematological toxicities of CAR T-cell therapies**

aplasia that is often refractory to treatment and translates into a high risk for infections and non-relapse mortality.

The final phase of haematotoxicity is observed 30 days after CAR T-cell infusion and describes prolonged or late-onset cytopenias.[5] To understand the clinical relevance of these later cytopenias, the presence or absence of antecedent count recovery must be considered (eg, patients with intermittent *vs* aplastic neutrophil recovery).[24] Patients with sustained neutropenia lasting into the second month after CAR T-cell infusion (eg, the aplastic phenotype) present with a very high risk for severe and even fatal infections.[12,14] Although patients with recurrent cytopenias (eg, the intermittent phenotype) can be repeatedly admitted to the hospital due to infectious events or transfusion needs, they also often exhibit good survival outcomes and a watch-and-wait approach to management can thus be reasonable.[24] Nonetheless, persistently low counts can prevent patients from being offered potentially efficacious post-relapse therapies, because cytopenias are common study exclusion criteria. Finally, any new-onset or unexplained cytopenias must raise concern for secondary malignancies, particularly treatment-emergent myeloid neoplasms, and should thus prompt a bone marrow examination.[25]

Expected incidence rate of ICAHT in clinical trials and the real-world setting

Several studies have reported on the incidence rates and quality of haematological side-effects of CAR T-cell therapy (table 1). In general, the expected rates of grade 3 or 4 cytopenias are very high, ranging between 28–65% (severe thrombocytopenia), 16–77% (severe anaemia), and 59–95% (severe neutropenia). Substantial heterogeneity was noted for the definition of prolonged cytopenias (eg, day 21 *vs* day 30 *vs* day 90), highlighting differences in the reporting of late cytopenias.[17] In terms of disease entity, the aplastic phenotype was more commonly encountered in patients with lymphoma (eg, large B-cell lymphoma or mantle cell lymphoma) compared with patients with multiple myeloma.[12–14] Furthermore, most studies showed increased haematotoxicity in patients receiving CAR T-cell products harbouring the CD28ξ endodomain compared with the 4-1BBξ endodomain.[7] This observation was corroborated by a matched–paired comparison of axicabtagene ciloleucel versus tisagenlecleucel from the DESCAR-T registry.[28] However, any direct comparisons of the incidence of haematotoxicity across clinical trials evaluating CAR T-cell products is complicated by substantial heterogeneity in disease entity (B-cell precursor acute lymphoblastic leukaemia, B cell non-Hodgkin lymphoma, and multiple myeloma), CAR T-cell product (CD28ξ *vs* 4-1BBξ), and cytopenia reporting (particularly for late cytopenias). A 2022 meta-analysis indicated an increased rate of high-grade cytopenias in patients with B-cell precursor acute lymphocytic leukaemia, probably as a result of bone marrow infiltration by leukaemic blasts and the extensive previous treatment lines.[29] When applying the new

EHA EBMT consensus grading (table 2), the incidence of severe or life-threatening early ICAHT was highest in patients with mantle cell lymphoma, followed by large B-cell lymphoma, and multiple myeloma (28% *vs* 23% *vs* 15%, respectively). However, the multivariable model suggested that the observed disease-specific differences more fundamentally reflect variability in underlying patient features (eg, disease burden and inflammation).[31]

Defining ICAHT

Initial clinical trials exploring CAR T-cell therapies primarily attributed cytopenias according to the common terminology criteria for adverse events (table 2). However, such a purely quantitative grading system fails to capture the unique quality of post-CAR T-cell haematotoxicity and does not reflect the risk of infections due to neutropenia. This risk is based not only on the depth of, but also the duration of severe neutropenia (eg, protracted neutropenia lasting longer than 7 days).[30] To account for these limitations, an expert panel from the EHA and EBMT developed a new grading system for ICAHT that separates early (days 0–30) and late (after day 30) ICAHT.[7] Early ICAHT assesses the duration of continuous severe (ANC <500/μL) or profound (ANC <100/μL) neutropenia and thereby closely mirrors the American Society of Clinical Oncology and Infectious Diseases Society of America guidelines for cancer-related infection risk.[30] The grading of early ICAHT follows the severity categories of mild, moderate, severe, and life-threatening—similar to the broadly implemented American Society for Transplantation and Cellular Therapy grading systems for CRS and ICANS. A 2024 study showed that the early ICAHT grading closely reciprocated the clinically relevant phenotypes of neutrophil recovery (panel 1).[31] Concomitantly, patients with severe or life-threatening ICAHT frequently displayed the aplastic neutrophil recovery phenotype, consistent with profound bone marrow aplasia in this small subset of patients. Although ICAHT severity was linked to clinically meaningful endpoints, such as infection, non-relapse mortality, transfusion use, duration of hospitalisation, and adverse treatment outcomes, the utility of the grading system still needs to be prospectively evaluated. Nonetheless, a standardised grading system has specific advantages, such as enabling comparability across disease entities, CAR T-cell products, and treatment settings.

Pathophysiology of haematotoxicity after CAR T-cell therapy

A range of clinical risk factors contribute to the development of cytopenias after CAR T-cell therapy, which can be broadly separated into host-related, disease-related, and treatment-related factors (appendix p 1). These factors provide crucial context for understanding the underlying pathophysiology of haematotoxicity. The heterogeneity of clinical variables associated with prolonged cytopenias shows that haematotoxicity is unlikely to be mediated by any one factor alone. Instead, a variety of features relating to the HSC reserve, the bone marrow microenvironment, systemic inflammatory mediators, and CAR T-cell expansion characteristics probably act together, either in concert or independently (eg, multifactorial origin; figure 2).

	Grade 1	Grade 2	Grade 3	Grade 4
Common terminology criteria for adverse events				
Neutropenia (ANC/μL)	<LLN–1500	<1500–1000	<1000–500	<500
Anaemia (Hb g/dL)	<LLN–10·0	<10·0–8·0	<8·0; transfusion	Life-threatening intervention
Thrombocytopenia (platelet count G/L)	<LLN–75	<75–50	<50–25	<25
ICAHT grading				
Early; 0–30 days after CAR T-cell infusion (ANC/μL)	<500* for 1–6 days	<500 for 7–13 days	<500 for ≥14 days; <100† for ≥7 days‡	Never above 500; <100 for ≥14 days
Late; 30 or more days after CAR T-cell infusion (ANC/μL)	<1500	<1000	<500	<100

Based on American Society of Clinical Oncology and Infectious Diseases Society of America consensus grading of cancer-related infection risk for severe neutropenia (ANC <500/μL), profound neutropenia (ANC <100/μL), and protracted neutropenia (≥7 days).[30] ANC=absolute neutrophil count. Hb=haemoglobin. LLN=lower limit of normal. *Severe neutropenia. †Profound neutropenia. ‡Protracted neutropenia.

Table 2: **Overview of haematotoxicity grading systems**

Panel 1: Phenotypes of neutrophil recovery

Quick recovery
Sustained neutrophil recovery without a second decline beneath an absolute neutrophil count (ANC) <1000/μL

Intermittent recovery
Neutrophil recovery (ANC >1500/μL) followed by a second decline beneath an ANC <1000/μL

Aplastic recovery
Continuous severe neutropenia (ANC <500/μL) for greater than or equal to 14 days

1) Role of the HSC reserve

Haematopoietic stem and progenitor cells (HSPCs) reside in a specialised niche in the bone marrow that is surrounded by endothelial and mesenchymal stromal cells, where they serve as precursors to a wide array of cells of the innate and adaptive immune systems.[32] The regenerative capacity of HSCs and their ability to respond to external stimuli in patients receiving CAR T-cell therapy is dependent on many factors, including the cumulative cytotoxic stress conferred by previous genotoxic chemotherapies (especially lenalidomide or alkylating agents, such as melphalan),[33,34] the process of natural ageing,[35] and direct or indirect interactions between the underlying disease and HSPCs.[36] The acquisition of somatic mutations due to these factors can facilitate the

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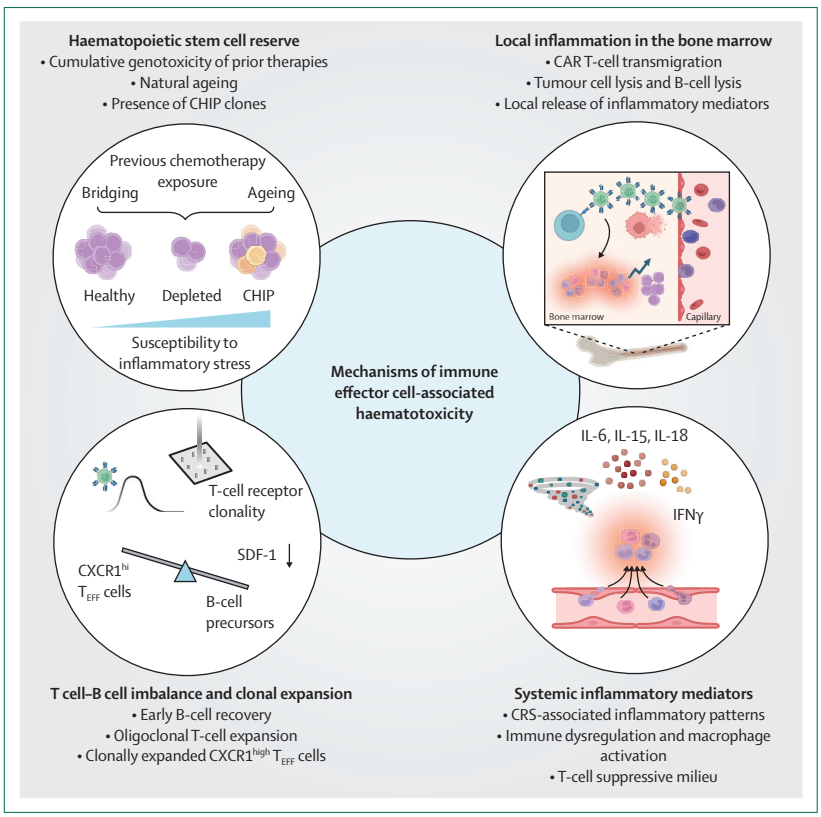

Figure 2: **Potential pathomechanisms of ICAHT**
CAR=chimeric antigen receptor. CHIP=clonal haematopoiesis of indeterminate potential. CRS=cytokine release syndrome. $CXCR1^{hi}$=high gene expression of CXCR1. ICAHT=immune effector cell-associated haematotoxicity. T_{EFF}=effector T cells.

development of age-related clonal haematopoiesis and clonal haematopoiesis of indeterminate potential (CHIP), which is defined by the manifestation of cancer-related somatic driver mutations with a variant allele frequency of greater than 2% in peripheral blood. The prevalence of CHIP is inherently age-dependent, with an expected rate of 10–20% in individuals 70 years or older.[37] However, prevalence is higher in patients with lymphoma compared with other older individuals (approximately 30% before autologous haematopoietic cell transplantation [HCT]) and the presence of CHIP has been associated with adverse treatment outcomes.[38] In patients receiving CAR T-cell therapy, the prevalence of CHIP has been described between 34% and 56%.[39–43] HSCs not only react to infections and inflammatory stimuli, but also serve as the foundation of the host immune response by replenishing specific immune cell populations.[44] Accordingly, the presence of clonal haematopoiesis might potentiate the host inflammatory response to CAR T cells. Furthermore, evidence from a preprint paper published in 2023 suggests that CHIP clones might be gradually selected for because they are more resistant to the deleterious effects of inflammation and ageing.[45] In line with this observation, clonal expansion of CHIP clones has been observed following CAR T-cell therapy, with a trend towards more pronounced late cytopenias in these patients.[39,46] This observation would indicate context-dependent selection of pre-existing CHIP clones following CAR T-cell therapy, which might be accelerated by specific genotypes (eg, *TP53*).[47]

2) Role of the bone marrow microenvironment

The bone marrow microenvironment is orchestrated by the complex interplay of cells and factors that regulate haematopoiesis, including mesenchymal stem cells, a vascular niche formed by endothelial cells and perivascular stromal cells, and adipocytes and bone lineage cells that contribute to the microenvironment's metabolic and structural dynamics.[32] Soluble factors, such as cytokines and growth factors, mediate crucial communication and regulatory pathways within this niche.[48] Kitamura and colleagues[49] reported that the bone marrow niche is severely disrupted in patients receiving CAR T-cell therapy with prolonged cytopenias, identifying an impairment of $CD271^{+}$ stromal cells by use of three dimensional imaging analyses from bone marrow biopsy specimens. Furthermore, the authors found that CXC chemokine ligand 12 (CXCL12; coding for SDF-1) and stem cell factor (SCF; coding for Kit ligand), both niche factors essential for haematopoietic recovery, were decreased in the bone marrow of patients with prolonged cytopenia, indicating reduced niche cell function. The presence of underlying bone marrow infiltration (eg, extranodal involvement of the lymphoma) probably disrupts the intricate balance within the niche. Bone marrow involvement is one of the strongest independent predictors of severe post-CAR T-cell haematotoxicity across several disease entities.[10,11,24] One potential explanation for this observation is the transmigration of CAR T cells to target cells within the bone marrow, resulting in local hyperinflammation and the release of cytokines and growth factors in close vicinity to haematopoietic progenitor cells. Even in the absence of lymphoma cells in the bone marrow, interactions between CAR T cells and endogenous $CD19^{+}$ or $BCMA^{+}$ B-cell precursor populations (eg, on-target off-tumour toxicity) might contribute to local inflammatory processes and microenvironmental alterations that subsequently result in prolonged cytopenias.

3) Role of systemic inflammatory mediators

Although inflammation-induced activation of HSCs and cytokines (such as IFN-γ) can cause HSCs to lose quiescence and proliferate in the short term, chronic exposure can lead to their functional impairment and depletion.[50] Specifically, IFN-γ has been shown to reduce stem cell cycling and plays a key regulatory role in the proliferation and differentiation of human HSPCs.[51,52] Chronic inflammation is particularly deleterious, causing long-term changes to the bone marrow microenvironment, promoting ageing-related changes, and potentially leading to bone marrow failure.[50]

In the context of CAR T-cell therapy, severe CRS and several inflammatory markers have been implicated in the development of severe haematotoxicity. Juluri and colleagues[23] found that higher peak IL-6 serum concentrations were associated with slower haematopoietic recovery and similar elevations of IL-6 concentrations have been observed locally within the bone marrow niche.[49] The authors also noted high serum TGF-β concentrations in patients with improved haematopoietic recovery; TGF-β is a pleiotropic cytokine that can mediate the proliferation of myeloid-producing HSCs.[53] Focusing on patients with aplastic neutrophil recovery after CAR T-cell therapy, serum proteomic studies revealed a signature displaying hallmarks of immune dysregulation and macrophage activation (eg, elevation of IL-15, IL-18, and MCP-1 concentrations), endothelial dysfunction (eg, increasing angiopoietin 2 to 1 ratio), and T-cell suppression (eg, upregulation of soluble T-cell checkpoint ligands).[24] Together with increased IFN-γ and serum ferritin concentrations in patients with aplastic neutrophil recovery, this study indicated some mechanistic overlap with immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), which also frequently presents with pancytopenia and is a well-characterised side-effect of CAR T-cell therapy.[54] Many of the perturbations of these systemic inflammatory mediators were already present before the application of CAR T cells, underlining the importance of pre-existing inflammation for the subsequent development of severe haematotoxicity. Patients with impaired haematopoietic function at baseline might be at particular risk of inflammation-mediated myelosuppression induced by the infusion of CAR T cells.[55]

The role of CAR T-cell expansion in driving cytopenias is not fully resolved and might be dependent on the pattern of cytopenia. Patients with biphasic neutrophil recovery (eg, recurrent neutrophil dips) displayed markedly higher CAR T-cell expansion and persistence compared with patients with aplastic recovery. Intermittent cytopenia might thus reflect extravasation of immune cells, including CAR T cells, into the periphery, bone marrow, and lymphomatous tissue. Conversely, immune dysregulation that is both inflammatory (eg, high IFN-γ and IL-18 concentrations) and T-cell suppressive (eg, upregulation of soluble T-cell checkpoint ligands) could explain the paradoxical finding of lower CAR T-cell expansion in patients with aplastic neutrophil recovery. These results suggest that CAR T-cell expansion is not the sole driver of cytopenias, but rather that CAR T-cell expansion exacerbates pre-existing inflammation, thereby inducing an injury to the bone marrow.

4) Role of clonal T cell expansion and T cell–B cell imbalances

An early correlative study of haematological toxicity following anti-CD19 CAR T-cell therapy showed perturbations of SDF-1 concentrations in patients with prolonged neutropenia.[8] SDF-1 is an essential chemokine for B-cell development and the trafficking of neutrophils and HSCs, and has been previously implicated in cases of late-onset neutropenia after B-cell depleting treatment with rituximab.[56] The authors postulate that early recovery of B cells after anti-CD19 CAR T-cell therapy might lead to alterations of SDF-1 concentrations in the bone marrow microenvironment, with subsequently reduced neutrophil egress from the bone marrow. Furthermore, the association between B-cell depleting therapies and neutropenia has been linked to the clonal expansion of T cells—most likely due to T-cell imbalances facilitated by diminished T cell–B cell interactions.[57] In line with this finding, detailed single-cell RNA and T-cell receptor (TCR) sequencing from a patient with acquired bone marrow failure following CAR T-cell therapy showed marked oligoclonal T-cell expansion, particularly of a $CD8^{+}$ $CD57^{+}$ T-cell population. This expansion was accompanied with a shift from multiclonal to oligoclonal TCR usage, with the degree of oligoclonality rivalling those of a reference population of patients with T-cell large granular lymphocytic leukaemia.[58] Similar clonal expansion events were noted by Strati and colleagues,[59] who observed an increase in the frequency of clonally expanded cytotoxic effector T cells with high gene expression of CXCR1 ($CXCR1^{hi}$) in patients with prolonged cytopenia following CAR T-cell therapy. These expanded effector T-cell subsets expressed high concentrations of IFN-γ and showed enrichment of cytokine signalling gene sets, while corresponding HSC populations in the same patients expressed IFN-γ response signatures.[59]

Management

Identifying patients with a high-risk profile for severe ICAHT

The CAR-HEMATOTOX score was developed to enable early risk-stratification into a high risk versus low risk of developing severe haematotoxicity following CAR T-cell therapy.[9] The score is calculated before initiation of lymphodepletion and incorporates the complete blood count (eg, ANC, haemoglobin, and platelet count) and two serum inflammatory markers (eg, C-reactive protein and ferritin). Patients deemed at high risk (score ≥2) displayed an increased rate of severe and prolonged neutropenia, severe thrombocytopenia, and anaemia compared with patients at low risk (score 0–1). Aside from severe ICAHT, high CAR-HEMATOTOX scores have also been linked to severe infections, increased non-relapse mortality, and poor treatment outcomes, indicating broad applicability of the score.[21] Furthermore, the score was validated for use in patients with multiple myeloma treated with anti-BCMA CAR T cells and patients with mantle cell lymphoma treated with brexucabtagene autoleucel (anti-CD19 CAR T cells).[10,11] Although the individual score components also appear to be relevant for adult and paediatric patients with

B cell acute lymphocytic leukaemia, many patients are classified as high risk based on a score threshold of 2 and it is probable that further refinements of the score are required for this disease entity.[60] The limitations of the score include its low positive predictive value (ie, it is better at ruling out than in) and it remains to be seen if the score is also predictive at earlier time points (ie, before leukapheresis), which would enable prophylactic collection of autologous CD34+ stem cells as a potential rescue strategy in patients with a very high risk of haematotoxicity.

Diagnostic algorithm

For patients with severe cytopenia before lymphodepletion, underlying bone marrow involvement should be strongly considered and confirmed with histopathological studies. Knowledge of the extent of bone marrow infiltration as a highly relevant risk factor can help with the interpretation of subsequent cytopenia trajectories and guide therapeutic strategies. Assessing the presence of pre-existing CHIP with next-generation sequencing is not, to date, a standard of care. However, it can be prudent to cryopreserve the bone marrow aspirate or peripheral blood mononuclear cells to enable testing for CHIP in case a patient develops secondary bone marrow failure after CAR T-cell therapy and, more generally, to contribute to our growing understanding of the proinflammatory role of CHIP in patients receiving CAR T-cell therapy.

Since cytopenias are to be expected in the first week after CAR T-cell infusion, we recommend initiating more comprehensive diagnostic studies in patients with persisting severe neutropenia beyond day 10.[7,61] A first step should include ruling out other pertinent causes of neutropenia, such as drug-induced myelosuppression (eg, co-trimoxazole and other antibiotics), vitamin deficiencies, and coincident infections (eg, viral infections or sepsis).[62] In patients with rapid elevation of serum ferritin concentrations, IEC-HS should be considered as an important differential diagnosis.[54] A more advanced investigation should be initiated in patients with severe or life-threatening early ICAHT and in those who are refractory to G-CSF (eg, absent neutrophil count recovery despite at least 5 days of G-CSF treatment). This examination should incorporate extended viral studies and bone marrow studies to rule out persistent infiltration (eg, progressive disease) and evaluate for signs of haemophagocytosis or myelodysplasia, which can emerge rapidly after CAR T-cell infusion.[25] However, the typical finding is a hypocellular marrow without dysplastic changes.[6] Because treatment-emerging myeloid neoplasms are a diagnostic concern after CAR T-cell therapy, in-depth cytogenetic studies and next-generation sequencing with a myeloid panel should be considered in case of any new-onset or unexplained cytopenia, or non-resolving ICAHT beyond day 30.

Therapeutic strategies

When CAR T-cell therapies first entered the clinical routine, there was a reluctance to apply growth factors for the management of cytopenias because preclinical studies had suggested that the use of granulocyte–macrophage colony-stimulating factor (GM-CSF) might promote inflammatory toxicity and induce neuroinflammation.[63] Because of these preclinical findings, G-CSF was commonly deferred until acute CAR T-cell immunotoxicities had abated (typically by the third week). However, several real-world studies have since shown that G-CSF can be given as early as the first week, or even prophylactically, with no statistically significant increase in the rate of grade 3 or higher CRS or ICANS.[64–67] For example, Lievin et al[65] showed that early G-CSF administration (starting at day 2) in patients with neutropenia was associated with a reduction in the rate of febrile neutropenia, with no negative effects on CAR T-cell expansion or clinical outcomes. A further retrospective study of 197 patients examined the effects of prophylactic G-CSF, with most patients receiving pegylated G-CSF before CAR T-cell therapy.[66] Although there was a slight increase in the rate of grade 2 (but not grade 3) CRS, prophylactic G-CSF was associated with faster neutrophil recovery and shorter intravenous antibiotic exposure.[66] Furthermore, the authors showed that the initiation of G-CSF in patients with grade 1 CRS did not exacerbate CRS severity. Nonetheless, these studies were not prospective and more research will be needed to further confirm the safety of early G-CSF and identify the optimal treatment protocol for each disease entity (eg, early *vs* prophylactic *vs* ANC-triggered and non-pegylated *vs* pegylated). Scores—such as the CAR-HEMATOTOX—could be useful to guide early G-CSF and anti-infective strategies and thereby could help to restrict these interventions to the patients who are most likely to benefit (eg, those at high risk with a score ≥2).[21]

Most patients receiving CAR T-cell therapy will ultimately either spontaneously recover their neutrophil counts or display prompt count improvement with G-CSF.[6,26] However, a minority of patients do not respond to G-CSF (<20%) and treatment of these patients can be clinically challenging, due to their high risk for life-threatening infections. If cryopreserved CD34+ stem cells are available from a previous autologous or allogeneic HCT, an HSC boost should be the preferred rescue strategy, due to the encouraging rates of engraftment.[68–70] However, a 2023 EHA and EBMT survey showed that HSC boosts were often not available, even when they were considered as a therapeutic avenue.[17] Patients with multiple myeloma could be an exception, because some younger patients might have collected additional cells for a potential second consolidative transplantation, as was shown by Mohan et al in a 2024 study.[71] Prophylactic stem cell collection in candidates for CAR T-cell therapy who are at high risk of developing severe haematotoxicity has been successfully

carried out in individuals,[69] but can be associated with additional costs and an increased logistic burden and should not delay the application of CAR T cells.[72] Other options for patients who are refractory to G-CSF include thrombopoietin receptor agonists, such as eltrombopag or romiplostim, although evidence is limited and it remains unclear if their use is superior to a watch-and-wait approach.[73,74] Both thrombopoietin receptor agonists and interferon-neutralising antibodies, such as emapalumab, would target the aberrant interferon signalling outlined above.[59] For patients with grade 3 or 4 ICAHT with a clear inflammatory stressor—such as IEC-HS[54]—and persistently increased inflammatory markers, a trial of anti-inflammatory agents, such as pulse-dose corticosteroids, or anti-cytokine therapies (eg, siltuximab or anakinra) can be attempted. If grade 4 ICAHT persists (<5% of patients[31]), allogeneic HCT can be offered as a last option. However, this treatment will invariably result in the eradication of CAR T cells and this decision should carefully weigh several factors: donor suitability and availability, the patient's goals of care, the possibility of spontaneous neutrophil count recovery, the risk of fatal infections, and the likelihood of disease recurrence.[61] When pursuing observation, optimising supportive strategies (eg, prophylactic anti-infectives, intravenous immunoglobulin therapy, and avoiding sick contacts) and obtaining an infectious disease consultation is recommended.

Conclusions and future perspectives

The past 5 years have seen increasing recognition of ICAHT as a distinct and clinically relevant side-effect of CAR T-cell therapy. By defining haematotoxicity, the EHA and EBMT consensus grading system provides a framework for severity-based best practice recommendations, similar to what already exists for CRS and ICANS.[3] Moreover, the grading provides clear criteria for the reporting of ICAHT, thus enabling standardised comparisons across disease entities and CAR T-cell products. Yet several unresolved clinical and translational research questions still remain (panel 2).

This Review has focused on CAR T cells, however, haematological toxicities are also among the most common side-effects of bispecific antibody therapies.[75] Future studies could evaluate the qualitative features of cytopenia with bispecific antibodies and study if the same risk factors apply. We anticipate that large multicentre studies will be needed to elucidate the effects of specific previous therapies, such as bendamustine, examine the influence of different lymphodepletion regimens, and establish whether transitioning CAR T-cell therapy into earlier treatment lines mitigates the risk of severe ICAHT. The diagnostic accuracy of the CAR-HEMATOTOX score could be further improved by integrating dynamic risk factors, such as inflammatory markers (eg, IL-6 and IFN-γ) or by making disease-specific adjustments. Potential applications of the score include restricting antibiotic prophylaxis or early G-CSF to patients at high risk, which would ideally be confirmed prospectively. Studying different ICAHT mitigation strategies in clinical trials will help to establish the optimal timing and sequence of G-CSF, thrombopoietin receptor agonists, and HSC boosts. Crucial clinical endpoints to consider include time to neutrophil recovery, the rate of febrile neutropenia and infections, but also other measures, such as antibiotic exposure and duration of hospitalisation.

Although translational efforts have provided some insights into the underlying mechanisms of ICAHT, it is

Panel 2: **Future clinical and translational research questions regarding haematological complications of chimeric antigen receptor (CAR) T-cell therapy**

Clinical research questions

- How does previous treatment before immune effector cell therapy shape the risk of developing immune effector cell-associated haematotoxicity (ICAHT) and is there a reduction of incidence rates when moving CAR T-cell therapy into earlier treatment lines?
- What is the contribution of lymphodepletion for the development of severe haematotoxicity and does bendamustine-based lymphodepletion reduce the incidence of cytopenias?
- Does the presence of clonal haematopoiesis before CAR T-cell therapy affect the subsequent development of cytopenias?
- Can the predictive capacity of the CAR-HEMATOTOX score be validated in a prospective manner and is the score helpful in guiding granulocyte colony-stimulating factor (G-CSF) and anti-infective therapies?
- What strategies can be used to better identify patients who will develop treatment-refractory bone marrow aplasia and what is the role of pro-inflammatory serum biomarkers, such as IL-6 or IFN-γ?
- Are there criteria that could guide the decision to prophylactically collect stem cells in specific candidates at high risk as a rescue strategy in case of severe haematoxicity?
- What is the optimal timepoint to initiate growth factor support and is there an advantage to applying pegylated versus non-pegylated G-CSF?
- Does early or prophylactic G-CSF reduce antibiotic exposure or the rate of severe infections?
- What is the incidence of ICAHT with other immune effector cell therapies, such as tumour-infiltrating lymphocytes or bispecific antibodies, and are the underlying risk factors similar?
- What is the relationship between ICAHT and the development of second primary malignancies, particularly treatment-emergent myeloid neoplasms?

Translational research questions

- Can a syngeneic mouse model be generated that reciprocates the unique qualities of CAR T-cell-related cytopenia?
- What is the role of CAR T cells in driving the expansion of clonal haematopoiesis clones into overt myeloid malignancy and are these clones more susceptible to CAR T-cell-mediated inflammation?
- How do cytokine release syndrome and inflammatory patterns specifically influence haematopoietic function?
- How do endogenous B-cell populations and their early recovery contribute to long-term cytopenias and do CAR T cells localise to the haematopoietic niche in the bone marrow?
- What precise mechanisms underlie the superior treatment outcomes in patients with intermittent neutrophil recovery?

Search strategy and selection criteria

We searched PubMed and MEDLINE for articles published between Jan 1, 2017, and Sept 30, 2023, by use of the search terms "chimeric antigen receptor", "CAR", "CAR-T", "CAR T-cell therapy", "bone marrow", "hematopoiesis", "cytopenias", "prolonged cytopenia", "delayed cytopenia", "hematotoxicity", "ICAHT", and "immune effector cell-associated hematotoxicity". We screened all studies arising from this search query and reviewed the relevant references cited in those articles. Studies had to be published in English. Abstracts were screened by the authors to establish the most relevant publications, which were included with all seminal studies in this Review.

unlikely that there is one unifying pathophysiology. Future preclinical studies will therefore have to take a panoply of host-related and disease-related features into account. Mechanistic studies will require structured sample collection that is harmonised across centres and should leverage emerging technologies, such as multi-omic and spatial transcriptomic approaches. Furthermore, the paucity of preclinical and animal models studying the effects of CAR T-cell therapy on haematopoiesis will need to be overcome, which would enable the systematic evaluation of novel therapeutics that ameliorate severe ICAHT. Ultimately, addressing these emerging research questions will require dedicated efforts that integrate multilateral collaborations, registry studies, and well-designed clinical trials. The latter should carefully evaluate specific management strategies, which would provide a blueprint for other immune effector cell therapies, like bispecific antibodies.

Contributors

KR and MS conceptualised this Review and wrote the methods. KR did the formal analysis and data visualisation and wrote the original draft. All authors did the investigation and reviewed, edited, read, and approved the final manuscript.

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References

1 Schett G, Mackensen A, Mougiakakos D. CAR T-cell therapy in autoimmune diseases. *Lancet* 2023; **402:** 2034–44.
2 Daei Sorkhabi A, Mohamed Khosroshahi L, Sarkesh A, et al. The current landscape of CAR T-cell therapy for solid tumors: mechanisms, research progress, challenges, and counterstrategies. *Front Immunol* 2023; **14:** 1113882.
3 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:** 625–38.
4 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:** 3024–33.
5 Jain T, Olson TS, Locke FL. How I treat cytopenias after CAR T-cell therapy. *Blood* 2023; **141:** 2460–69.
6 Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica* 2021; **106:** 978–86.
7 Rejeski K, Subklewe M, Aljurf M, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. *Blood* 2023; **142:** 865–77.
8 Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant* 2019; **54:** 1643–50.
9 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:** 2499–513.
10 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:** 1699–710.
11 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:** 88.
12 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:** 121.
13 Cordeiro A, Bezerra ED, Hirayama AV, et al. Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. *Biol Blood Marrow Transplant* 2020; **26:** 26–33.
14 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.

15 Cordas dos Santos DM, Tix T, Rejeski K. Infections Drive Non-Relapse Mortality Following CAR-T Therapy across Disease Entities and CAR Products–a Meta-Analysis of Clinical Trials and Real-World Studies. *Blood* 2023; **142** (suppl 1): 1064 (abstr).

16 Vic S, Thibert J-B, 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:** 1573–85.

17 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:** e889.

18 Bücklein V, Perez A, Rejeski K, et al. Inferior outcomes of EU versus US patients treated with CD19 CAR-T for relapsed/refractory large B-cell lymphoma: association with differences in tumor burden, systemic inflammation, bridging therapy utilization, and CAR-T product use. *HemaSphere* 2023; **7:** e907.

19 Iacoboni G, Navarro V, Martín-López AA, et al. Recent bendamustine treatment before apheresis has a negative impact on outcomes in patients with large B-cell lymphoma receiving chimeric antigen receptor T-cell therapy. *J Clin Oncol* 2024; **42:** 205–17.

20 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:** 2872–83.

21 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:** e004475.

22 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:** e858.

23 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:** 2055–68.

24 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:** eadg3919.

25 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:** 113.

26 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:** 3776–87.

27 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:** e006406.

28 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:** 2145–54.

29 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:** 2951–65.

30 Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA Clinical Practice Guideline Update. *J Clin Oncol* 2018; **36:** 3043–54.

31 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; published online Jan 4. https://doi.org/10.1182/bloodadvances.2023011767.

32 Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature* 2014; **505:** 327–34.

33 Danylesko I, Shimoni A. Second malignancies after hematopoietic stem cell transplantation. *Curr Treat Options Oncol* 2018; **19:** 9.

34 Saleem K, Franz J, Klem ML, et al. Second primary malignancies in patients with haematological cancers treated with lenalidomide: a systematic review and meta-analysis. *Lancet Haematol* 2022; **9:** e906–18.

35 de Haan G, Lazare SS. Aging of hematopoietic stem cells. *Blood* 2018; **131:** 479–87.

36 Maswabi BC, Molinsky J, Savvulidi F, et al. Hematopoiesis in patients with mature B-cell malignancies is deregulated even in patients with undetectable bone marrow involvement. *Haematologica* 2017; **102:** e152–55.

37 Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science* 2019; **366:** eaan4673.

38 Gibson CJ, Lindsley RC, Tchekmedyian V, et al. Clonal hematopoiesis associated with adverse outcomes after autologous stem-cell transplantation for lymphoma. *J Clin Oncol* 2017; **35:** 1598–605.

39 Panagiota V, Kerschbaum JF, Penack O, et al. Clinical implications and dynamics of clonal hematopoiesis in anti-CD19 CAR T-cell treated patients. *HemaSphere* 2023; **7:** e957.

40 Miller PG, Sperling AS, Brea EJ, et al. Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. *Blood Adv* 2021; **5:** 2982–86.

41 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:** 1941–46.

42 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:** 385–93.

43 von Bonin M, Jambor HK, Teipel R, et al. Clonal hematopoiesis and its emerging effects on cellular therapies. *Leukemia* 2021; **35:** 2752–58.

44 King KY, Goodell MA. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. *Nat Rev Immunol* 2011; **11:** 685–92.

45 Jakobsen NA, Turkalj S, Zeng AGX, et al. Selective advantage of mutant stem cells in clonal hematopoiesis occurs by attenuating the deleterious effects of inflammation and aging. *bioRxiv* 2023; published online Sept 14. https://doi.org/10.1101/2023.09.12.557322.

46 Hamilton MP, Sworder BJ, Alig SK, et al. CAR19 therapy drives expansion of clonal hematopoiesis and associated cytopenias. *Blood* 2023; **142** (suppl 1): 360 (abstr).

47 Weeks LD, Ebert BL. Causes and consequences of clonal hematopoiesis. *Blood* 2023; **142:** 2235–46.

48 Pinho S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. *Nat Rev Mol Cell Biol* 2019; **20:** 303–20.

49 Kitamura W, Asada N, Naoi Y, et al. Bone marrow microenvironment disruption and sustained inflammation with prolonged haematologic toxicity after CAR T-cell therapy. *Br J Haematol* 2023; **202:** 294–307.

50 Leimkühler NB, Schneider RK. Inflammatory bone marrow microenvironment. *Hematology Am Soc Hematol Educ Program* 2019; **2019:** 294–302.

51 de Bruin AM, Demirel Ö, Hooibrink B, Brandts CH, Nolte MA. Interferon-γ impairs proliferation of hematopoietic stem cells in mice. *Blood* 2013; **121:** 3578–85.

52 Morales-Mantilla DE, King KY. The role of interferon-gamma in hematopoietic stem cell development, homeostasis, and disease. *Curr Stem Cell Rep* 2018; **4:** 264–71.

53 Challen GA, Boles NC, Chambers SM, Goodell MA. Distinct hematopoietic stem cell subtypes are differentially regulated by TGF-beta1. *Cell Stem Cell* 2010; **6:** 265–78.

54 Hines MR, Knight TE, McNerney KO, et al. Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome. *Transplant Cell Ther* 2023; **29:** 438.e1–16.

55 Read JA, Rouce RH, Mo F, Mamonkin M, King KY. Apoptosis of hematopoietic stem cells contributes to bone marrow suppression following chimeric antigen receptor T cell therapy. *Transplant Cell Ther* 2023; **29:** 165.e1–7.

56 Dunleavy K, Hakim F, Kim HK, et al. B-cell recovery following rituximab-based therapy is associated with perturbations in stromal derived factor-1 and granulocyte homeostasis. *Blood* 2005; **106:** 795–802.

57 Dunleavy K, Tay K, Wilson WH. Rituximab-associated neutropenia. *Semin Hematol* 2010; **47:** 180–86.

58 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:** 2175–79.

59 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 IFNγ-expressing CD8 T cells. *Cell Rep Med* 2023; **4:** 101158.

60 McNerney KO, Fabrizio VA, Talleur AC, et al. Risk factors and outcomes for hematotoxicity following tisagenlecleucel for pediatric B-acute lymphoblastic leukemia. *Blood* 2023; **142** (suppl 1)**:** 2133 (abstr).

61 Rejeski K, Subklewe M, Locke FL. Recognizing, defining, and managing CAR-T hematologic toxicities. *Hematology Am Soc Hematol Educ Program* 2023; **2023:** 198–208.

62 Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. *Hematology Am Soc Hematol Educ Program* 2017; **2017:** 187–93.

63 Sterner RM, Sakemura R, Cox MJ, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood* 2019; **133:** 697–709.

64 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:** e399–402.

65 Liévin 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:** 431–39.

66 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:** 146.

67 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:** 653–58.

68 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:** 4719–25.

69 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:** 555–59.

70 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:** 4715–18.

71 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; published online Feb 15. https://doi.org/10.1038/s41409-024-02233-2.

72 Chhabra S, Thapa B, Szabo A, et al. Utilization and cost implications of hematopoietic progenitor cells stored for a future salvage autologous transplantation or stem cell boost in myeloma patients. *Biol Blood Marrow Transplant* 2020; **26:** 2011–17.

73 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:** 537–40.

74 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:** 538–46.

75 de Assis LH, Fassi DE, Hutchings M. Bispecific antibody therapies. *Hematology Am Soc Hematol Educ Program* 2023; **2023:** 216–22.