Recognizing, defining, and managing CAR-T hematologic toxicities

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Autologous CAR-T cell therapy (CAR-T) has improved outcomes for patients with B-cell malignancies. It is associated with the well-described canonical toxicities cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which may be abrogated by corticosteroids and the anti-IL6 receptor antagonist tocilizumab. Practitioners and researchers should be aware of additional toxicities. Here we review current understanding and management of hematologic toxicities after CAR-T, including cytopenias, coagulopathies, bleeding and clotting events, hemophagocytic-lymphohistiocytosis, and tumor lysis syndrome. We pay particular attention to cytopenias, recently termed immune effector cell-associated hematological toxicity (ICAHT). While the "H" is silent, hematotoxicity is not: ICAHT has the highest cumulative incidence of all immune adverse events following CAR-T. Early cytopenia (day 0–30) is closely linked to lymphodepleting chemotherapy and CRS-related inflammatory stressors. Late ICAHT (after day 30) can present either with or without antecedent count recovery (e.g., "intermittent" vs "aplastic" phenotype), and requires careful evaluation and management strategies. Growth factor support is the mainstay of treatment, with recent evidence demonstrating safety and feasibility of early granulocyte colony-stimulating factor (G-CSF) (e.g., within week 1). In G-CSF refractory cases, autologous stem cell boosts represent a promising treatment avenue, if available. The CAR-HEMATOTOX scoring system, validated for use across lymphoid malignancies (B-NHL, multiple myeloma), enables pretherapeutic risk assessment and presents the potential for risk-adapted management. Recent expert panels have led to diagnostic scoring criteria, severity grading systems, and management strategies for both ICAHT and the recently termed immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), now clarified and defined as a distinct entity from CRS.

LEARNING OBJECTIVES

- Review the classifications, categories, incidence, and management of ICAHT
- Evaluate baseline and postinfusional risk factors for prolonged cytopenia and infectious complications
- Characterize further hematologic complications of CAR-T, including coagulopathies, bleeding and thrombosis, IEC-HS, and tumor lysis syndrome

Introduction

Chimeric antigen receptor (CAR) T-cell therapy has altered the treatment landscape for an ever-increasing number of relapsed and refractory B-cell malignancies,[1-7] but it requires specialized attention to recognize and manage a unique toxicity profile. Next to CRS and ICANS as prototypical CAR-T side effects, additional hematologic toxicities are both frequent and clinically relevant.[8] Cytopenia following CAR-T, recently termed immune effector cell-associated hematological toxicity (abbreviated as ICAHT and pronounced "eye-cat") is perhaps the most common noncanonical CAR-T toxicity.[9] A less frequently observed hematologic complication outside of CRS is a distinct hemophagocytic syndrome, recently termed immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), which often manifests following resolution of CRS. Coagulopathies are common after CAR-T with both bleeding and thrombotic events experienced in some patients. Tumor lysis syndrome can manifest, although clinical impact is rare.

Here, we present a summary of our current understanding of the manifestations and management of these complications following CAR-T. This information is intended to allow practitioners to recognize and manage these complications promptly, to inform translational investigators trying to elucidate their mechanisms and optimal management approaches, and to prompt experts to action in further standardization of definitions and management algorithms.

CLINICAL CASE

A 62-year-old man with relapsed/refractory mantle cell lymphoma (MCL) was referred for CD19-directed CAR-T therapy with brexucabtagene autoleucel (brexu-cel). His prior disease course included chemoimmunotherapy, autologous transplantation, and ibrutinib. Chemotherapy bridging was employed during manufacturing. At lymphodepletion, his laboratory studies were notable for an elevated serum LDH, increased serum inflammatory markers (CRP 4.1 mg/dL, ferritin 881 ng/mL), and bilineage cytopenia (hemoglobin 8.8 g/dL, platelets 122 G/L). Baseline risk assessment was performed using the CAR-HEMATOTOX score, a risk stratification tool comprised of markers of hematopoietic function and baseline inflammation, with this patient presenting with a high-risk score of 4. Bone marrow studies revealed ~70% cellular involvement by blastoid MCL. On day 2 following CAR-T, the patient developed fever and progressive hemodynamic and respiratory insufficiency (maximal CRS grade 3), which resolved over the course of several days to grade 1 with administration of tocilizumab and corticosteroids. He also developed mild neurocognitive impairment on day 5 with a minimal ICE score of 8 (ICANS grade 1), which resolved on day 7. Following a rapid taper of steroids, on day 10, he presents with pronounced pancytopenia (ANC 0.1 G/L, Hb 7.1 g/dL, platelets 8 G/L).

Cytopenia after CAR-T: immune effector cell-associated hematological toxicity

Profound and/or prolonged cytopenias can predispose patients to significant infectious complications,[10] result in extended hospital stays,[11] and prevent subsequent salvage therapies at relapse.[12] However, the underlying pathophysiology remains enigmatic. While early cytopenia is expected after lymphodepleting chemotherapy, low counts can last weeks, months, or even years after CAR-T.[13] Neutrophil recovery typically follows either a biphasic or an aplastic trajectory (Figure 1).[8,14,15] Understanding underlying risk factors for hematotoxicity is critical for the application of risk-adapted management strategies.[9]

Incidence of ICAHT from pivotal trials to real-world evidence

Direct comparison of the incidence of post-CAR-T hematotoxicity, including cytopenias, across trials, and disease entities, is difficult due to differences in trial design, CAR construct, cohort size, and patient population. However, the observed degree and duration of hematotoxicity varies depending on the disease subtype (B-cell precursor acute lymphoblastic leukemia, B-NHL, multiple myeloma) and target antigen (CD19, BCMA) (Table 1). A recent meta-analysis demonstrated higher incidence of post-CAR-T cytopenia in BCP-ALL, likely related to extensive bone marrow infiltration or more intensive prior therapy.[16] High rates of cytopenia have also been noted for MCL, in line with the generally high toxicity burden in these

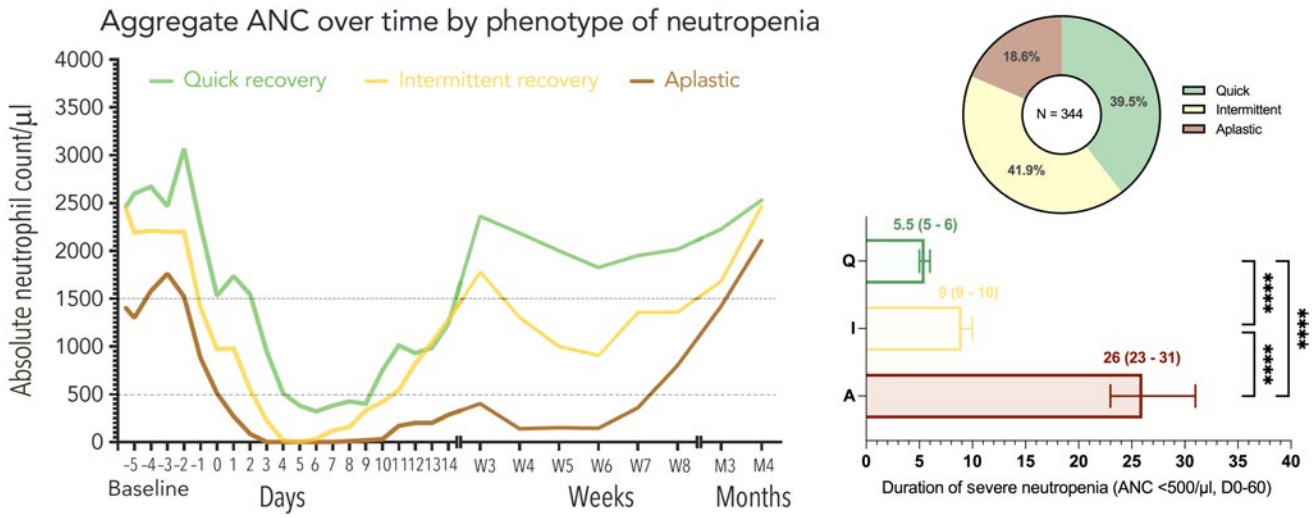

Figure 1. Phenotypes of neutrophil recovery following CAR T-cell therapy. Left panel: Quick recovery is defined as sustained neutrophil recovery without a second dip below an ANC <1000/µL. Intermittent neutrophil recovery (ANC >1500/µl) is followed by a second dip with an ANC <1000/µL after day 21. Aplastic is continuous severe neutropenia (ANC <500/µL) ≥14 days. (Adapted with permission from Rejeski et al., Blood. 2021.[8]) Right panel: Pie chart shows the relative distribution of neutrophil recovery phenotypes in a cohort of 344 relapsed/refractory LBCL patients treated with axi-cel or tisa-cel in a real-world setting. The duration of severe neutropenia (ANC <500/µL) during the first 60 days following CAR-T infusion is shown on the bottom. (Adapted with permission from Rejeski et al., ASH annual meeting 2022, abstract number 1987[21]). ANC, absolute neutrophil count.

Table 1. Incidence of post CAR-T cytopenias in clinical trials

Trial/product	Disease	Target/endodomain/vector	Lymphodepletion	Grade ≥3 neutropenia, %	Grade ≥3 thrombocytopenia, %	Grade ≥3 anemia, %	Reference
ZUMA-3 Brexu-cel	BCP-ALL	CD19/CD28z/RV	Flu 25 mg/m^2 × 3 Cy 900 mg/m^2 × 1	27%	30%	49%	Shah et al. Lancet 2021[3]
ZUMA-1 Axi-cel	LBCL	CD19/CD28z/RV	Flu 30 mg/m^2 × 3 d Cy 500 mg/m^2 × 3 d	78%	38%	43%	Locke et al. Lancet Oncol 2019[73]
JULIET Tisa-cel	LBCL	CD19/4–1BB/LV	Flu 25 mg/m^2× 3 d Cy 250 mg/m^2× 3 d	33%	28%	39%	Schuster et al. NEJM 2019[74]
TRANSCEND Liso-cel	LBCL	CD19/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	60%	27%	37%	Abramson et al. Lancet 2020[75]
ZUMA-7 Axi-cel	LBCL	CD19/CD28z/RV	Flu 30 mg/m^2× 3 d Cy 500 mg/m^2× 3 d	69%	15%	30%	Locke et al. NEJM 2022[1]
TRANSFORM Liso-cel	LBCL	CD19/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	82%	50%	52%	Abramson et al. Blood 2023[2]
ZUMA-2 Brexu-cel	MCL	CD19/CD28z/RV	Flu 30 mg/m^2× 3 d Cy 500 mg/m^2× 3 d	85%	51%	50%	Wang et al. NEJM 2020[4]
ELARA Tisa-cel	FL	CD19/4–1BB/LV	Flu 25 mg/m^2× 3 d Cy 250 mg/m^2× 3 d	32%	9%	13%	Fowler et al. Nat Med 2022[76]
ZUMA-5 Axi-cel	FL	CD19/CD28z/RV	Flu 30 mg/m^2× 3 d Cy 500 mg/m^2× 3 d	33%	9%	25%	Jacobson et al. Lancet Oncol 2022[77]
KarMMa-1 Ide-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	89%	52%	60%	Munshi et al. NEJM 2021[78]
KarMMa-3 Ide-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	76%	42%	51%	Rodriguez-Otero et al. NEJM 2023[79]
CARTITUDE-1 Cilta-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	95%	60%	68%	Berdeja et al. Lancet 2021[80]
CARTITUDE-4 Cilta-cel	MM	BCMA/4–1BB/LV	Flu 30 mg/m^2× 3 d Cy 300 mg/m^2× 3 d	90%	41%	36%	San-Miguel et al. NEJM 2023[81]

Cytopenias are graded according to clinical trial reporting (common terminology of adverse events—CTCAE).
Axi-cel, axicabtagene ciloleucel; BCMA, B-cell maturation antigen; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; brexu-cel, brexucabtagene autoleucel; CD, cluster of differentiation; cilta-cel, ciltacabtagene autoleucel; cy, cyclophosphamide; d, day; FL, follicular lymphoma; flu, fludarabine; ide-cel, idecabtagene vicleucel; G, grade; MCL, mantle cell lymphoma; MM, multiple myeloma; LBCL, large B-cell lymphoma; LV, lentiviral vector; liso-cel, lisocabtagene maraleucel; RV, γ-retroviral vector; tisa-cel, tisagenlecleucel.

patients.[17-19] Conversely, CAR-T trials for follicular lymphoma demonstrated low rates of hematotoxicity (Table 1), although real-world evidence is needed to confirm. When considering the co-stimulatory domain, matched comparison has revealed increased cytopenias in patients receiving CAR products harboring a CD28z as opposed to 4-1BB co-stimulatory domain.[16,20]

Real-world studies have confirmed the high rate of grade 3 or higher hematological toxicity and especially prolonged cytopenias following both CD19- and BCMA-directed CAR T-cell therapy (Table 2). Detailed studies on the nature of CAR-T-related cytopenias have shed light on the biphasic pattern of neutropenia, with second or even multiple decreases.[14] There are three distinct *phenotypes* of post-CAR-T neutrophil recovery (Figure 1).[8] These range from transient lymphodepletion-associated cytopenia ("quick") to the aforementioned biphasic course ("intermittent") and the clinically challenging "aplastic" phenotype associated with high morbidity and mortality.[15,21] The relative distribution of these phenotypes after CAR-T therapy is approximately 40%, 40%, and 20% (quick vs intermittent vs aplastic). Patients with the aplastic phenotype are often refractory to G-CSF and can develop prolonged neutropenia (Figure 1 bottom right shows median duration of severe neutropenia is 26 days). Interestingly, biphasic neutrophil recovery is linked to favorable treatment outcomes and higher levels of CAR T-cell expansion and persistence.[21] Of note, the thrombocytopenic nadir is commonly observed in the second month following CAR-T infusion.[8]

Cytopenias can persist long after lymphodepletion and resolution of CRS and ICANS. However, there is marked heterogeneity in the reporting and definitions of these long-term hematological side effects across studies. To address this, an expert panel recently developed a consensus grading system for early (day 0-30) and prolonged/late (after day +30 and day +90 respectively) ICAHT (Table 3). These clear definitions will ease reporting in trials, enable comparative studies of ICAHT severity across disease entities and CAR products, and provide a basis for severity-based management recommendations.

Short-term management of ICAHT using granulocyte colony-stimulating factor (G-CSF)

The case highlights a key decision point in managing early ICAHT: namely, when to initiate G-CSF and whether to defer G-CSF in case of coincident immunotoxicity (e.g., severe CRS

Table 2. Definition and incidence of prolonged cytopenias in the real-world setting

Reference	Disease	Sample size	Product	Definition of prolonged, day	Neutropenia	Thrombocytopenia	Comments
Nahas et al. Leuk Lymph 2020[82]	LBCL	21	Axi-cel	42	38%	-	2 cases of MDS
Strati et al. Haematologica 2021[83]	LBCL	31	Axi-cel	30	29%	42%	MDS (*n*=4)**
Fried et al. BMT 2019[14]	ALL, B-NHL	35	Local product/ CD19/CD28	42	62%	44%	Biphasic neutropenia and thrombocytopenia; proposed mechanism for late CART cytopenia: SDF-1 alterations
Cordeiro et al. BBMT 2020[13]	ALL, B-NHL, CLL	86	Local product/ CD19/4-1BB	90	16%	-	4 cases of MDS, long-lasting nature of cytopenia after CAR-T infusion
Jain et al. Blood Adv 2020[28]	BCL, ALL MM	83	Axi-cel, tisa-cel, local product	90	20%	10%	Delayed hematopoietic recovery associated with high-grade CRS/ICANS, MDS (*n*=1)*
Rejeski et al. Blood 2021[8]	LBCL	235	Axi-cel, tisa-cel	21	64%	-	Description of 3 typical neutrophil recovery phenotypes; thrombo-cytopenic nadir in month 2; development of CAR-HEMATOTOX score with independent validation
Wang et al. Front Oncol 2021[84]	ALL	76	Local product/ CD19; CD22/ 4-1BB	80	70%	48%	
Logue et al. Haematologica 2021[41]	LBCL	85	Axi-cel	30	30%	26%	Description of long-term immune reconstitution in LBCL patients treated with axi-cel
Logue et al. Blood Adv 2022[42]	MM	52	Ide-cel	30	39%	51%	Real-world data on hematotoxicity in multiple myeloma
Juluri et al. Blood Adv 2022[53]	ALL, B-NHL, CLL	173	Local product/ CD19/4-1BB	28	9%	14%	F/U (40M): persistent neutropenia (9%) and thrombocytopenia (14%); association of hematotoxicity with high-grade CRS and CRS-related inflammatory patterns
Bethge et al. Blood 2022[85]	LBCL	319	Axi-cel, tisa-cel	28/100	26%/10%	67%/32%	Defined as absence of count recovery; delayed hematopoietic recovery associated with NRM
Bachy et al. Nat Med 2022[20]	DLBCL	418	Axi-cel, tisa-cel	30/90	17%/6%	16%/5%	Matched-paired comparison of CAR products; increased hematotoxicity incidence with axi-cel > tisa-cel
Penack et al. JITC 2023[86]	LBCL	398	Axi-cel, tisa-cel	30/100	severe (CTC grade ≥3) cytopenia: 9%/12%		Association between number of prior treatment lines and incidence of cytopenia

Axi-cel, axicabtagene ciloleucel; ALL, acute lymphoblastic leukemia; BCL, B-cell lymphoma; BCMA, B-cell maturation antigen; B-NHL, B-cell non-Hodgkin lymphoma; brexu-cel, brexucabtagene autoleucel; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; d, day; DLBCL, diffuse large B-cell lymphoma; F/U, follow-up; G, grade; ide-cel, idecabtagene vicleucel; ICANS, immune effector cell-associated neurotoxicity syndrome; M, month; M1, neutropenia/thrombocytopenia at 1 month; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NRM, non-relapse mortality; LBCL, large B-cell lymphoma; SDF-1, stromal cell-derived factor 1; tisa-cel, tisagenlecleucel.

*MDS diagnosed in relapse after CAR-T-cell treatment.

**No difference in MDS incidence between patients with and without >G3 cytopenia at M1.

Adapted with permission from Rejeski, Subklewe et al, Blood. 2023.[9]

Table 3. Novel ICAHT grading

Grading	I	II	III	IV
Early ICAHT (day 0–30)				
ANC ≤ 500/µL	<7 days	7–13 days	≥14 days	Never above 500/µL
ANC ≤ 100/µL	-	-	≥7 days	≥14 days
*Late ICAHT (after day +30)**				
ANC ≤ 1500/µL				
ANC ≤ 1000/µL				
ANC ≤ 500/µL				
ANC ≤ 100/µL				

*Measured ≥2 time points or non-transient neutropenia.

Adapted from Rejeski et al, Blood 2023 with permission.[9]

or ICANS, typically during the first 2 weeks). Hesitation to administer G-CSF stems from preclinical data suggesting that GM-CSF may exacerbate toxicities.[22] However, retrospective analyses from real-word data sets have demonstrated an acceptable safety profile with early G-CSF without increases in the rate of high-grade (e.g., ASTCT grade 3 or higher) CRS or ICANS.[23-27] For example, Miller et al showed that patients receiving prophylactic G-CSF prior to CAR-T infusion (mostly pegylated G-CSF) displayed faster neutrophil recovery, comparable treatment outcomes, and similar rates of severe ICANS.[26] Importantly, patients presenting with low-grade toxicity did not exhibit worsening CRS severity with G-CSF. A separate study by Lievin et al found that early G-CSF administration (day +2) reduced febrile neutropenia without increased high-grade CRS or ICANS.[25] Notably, G-CSF did not impact CAR-T expansion or efficacy.[24,25] Taken together, these data support early G-CSF in high-risk patients to shorten severe neutropenia and prevent infections. Nonetheless, the optimal day of initiation and G-CSF protocol (prophylactic vs early; pegylated vs non-pegylated) in the context of CAR-T remains unclear. It must be noted that most CAR-T patients (>80%) will adequately respond to growth factor support with count recovery.[12,28]

CLINICAL CASE (continued)

On day 21, the patient had continued pancytopenia despite daily G-CSF and was transfusion-dependent for platelets and red cells. He developed hospital-acquired pneumonia and received broad anti-infective treatment. Bone marrow studies demonstrated aplasia and no MCL. Viral causes and substrate deficiency were ruled out. Myelotoxic co-medications were paused.

Clinical management of G-CSF refractory ICAHT cases

Diagnostic evaluation

Cases of ICAHT in which patients do not respond to G-CSF can be challenging, and this typifies the aplastic neutrophil recovery phenotype.[8,12] For diagnostic workup, a judicious incremental approach is warranted (Table 4). A first diagnostic tier should rule out other causes of BM insufficiency, including medications, viral infections, substrate deficiency, and severe IEC-HS (further described later). In patients without prior prophylactic G-CSF, we advocate initiation of G-CSF support on day 5-7 in neutropenic patients, particularly those with a high baseline CAR-HEMATOTOX score and in case the first diagnostic tests are inconclusive. If counts have not recovered despite G-CSF support, BM aspiration and biopsy should be employed no later than day 28 to rule out persistent BM infiltration (e.g. progression), perform IEC-HS diagnostics, and evaluate for dysplasia indicative of underlying myeloid dyscrasias which can evolve rapidly following CAR-T infusion.[29] The longer cytopenia persists beyond CAR-T infusion, the greater the impetus to perform in-depth cytogenetic studies and/or next-generation sequencing (myeloid panel). This is particularly important for workup of prolonged (day 30-90) and late (beyond day 90) cases of marrow aplasia or new-onset cytopenias long after CAR-T infusion.

Therapeutic interventions for severe and/or persistent ICAHT

In G-CSF refractory cases with an available cryopreserved autologous or allogeneic stem cell product from a prior treatment line (Figure 2), hematopoietic cell boosts should be strongly considered given their favorable safety profile and encouraging engraftment rates.[30-34] Unfortunately, these are available in only a minority of cases, with myeloma patients sometimes having extra stem cells for a potential second consolidative transplant.[35] Other options include thrombopoietin receptor agonists (TPO-RA) such as eltrombopag or romiplostim, though the data are restricted to a few small case series.[36-38] The potential improvement of hematopoietic function would mirror the efficacy of TPO-RA in other cases of acquired BM failure.[40] If the underlying etiology is deemed associated with inflammation or is HLH-like in nature, anti-inflammatory measures such as pulse-dose steroids or anticytokine therapy with anakinra or tocilizumab can be pursued. If the options described above do not facilitate count recovery and grade 4 ICAHT persists, allogeneic hematopoietic cell transplantation (allo-HCT) represents the last resort. However, gradual count recovery can occur over weeks to months, and allo-HCT will inevitably eradicate CAR T-cells. Before commencing with allograft, it is imperative to carefully consider all factors including time from CAR-T, the possibility of spontaneous count recovery, the risk for fatal infections, the likelihood of disease progression, donor suitability/availability, and the patient's goals of care.[28,41,42] Regardless of the treatment

Table 4. Diagnostic workup

Diagnostic category	Included diagnostic tests	When to initiate	Additional comments
Basis workup (tier 1)	• Check medication list for myelotoxic co-medications • Rule out active infections: blood cultures, procalcitonin • Vitamin deficiency: B12, folic acid • Consider secondary HLH/MAS: serum ferritin	In case of severe neutropenia (ANC <500/µL) beyond day +7 after CAR-T infusion	Low threshold to perform (minimal workup)
Advanced workup in case of severe ICAHT (tier 2)	• Bone marrow aspiration and biopsy • Advanced viral studies (parvovirus B19, CMV)	Grade 3 or higher ICAHT beyond day +14	Especially in patients with underlying marrow infiltration
Clinical suspicion for therapy-related myeloid neoplasm	Immunohistochemistry, flow cytometry, cytogenetics; next-generation sequencing (myeloid panel)	In case of persistent bone marrow aplasia beyond 1 month; unclear and/or new-onset cytopenia; cytopenia refractory to therapeutic measures	t-MN after CAR-T therapy is an emerging field of study*

ANC, absolute neutrophil count; CMV, cytomegaly virus; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICAHT, immune effector cell-associated hematotoxicity; t-MN, therapy-related myeloid neoplasm.

*Incidence rate as high as 6% of t-MN after CAR T-cell infusion (see Gurney et al., EHA 2023; abstract number S263[87]).

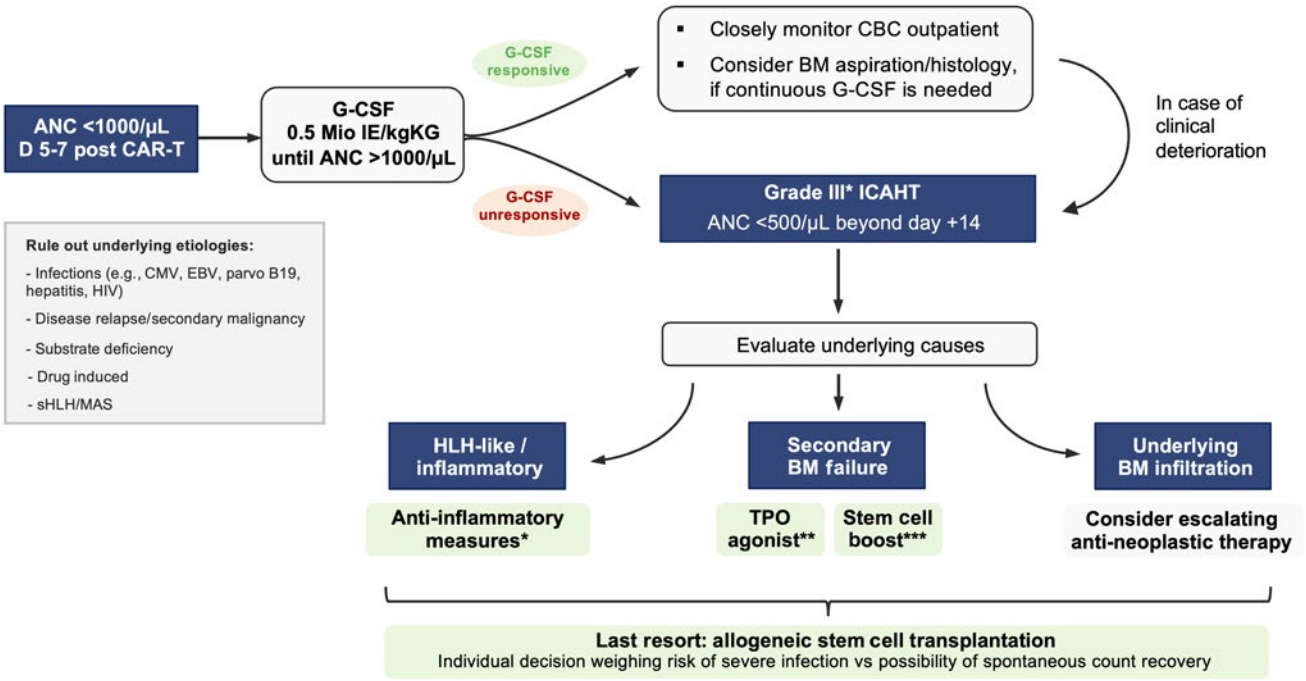

Figure 2. Treatment algorithm for immune effector cell associated hematotoxicity. *Consider dexamethasone-pulse (20 mg over 4 days) or anticytokine-therapy (e.g., anakinra or tocilizumab). **Consider eltrombopag (e.g., 50 mg×7 days). ***If available, contact apheresis unit.

strategy, mitigating the risk of severe infections with adequate and broad anti-infective therapy is critical. Fatal infections are possible and represent the main driver of non-relapse mortality.[11,15,43,44] Due to the broad spectrum of opportunistic pathogens, infectious disease consultation is recommended.

Moving toward risk-adapted management of ICAHT using the CAR-HEMATOTOX score

The management of CAR-T-related toxicities ideally should be tailored to the patient's individual risk profile. To this end, the CAR-HEMATOTOX (HT) score was developed and externally validated to predict severe hematotoxicity in relapsed and/or refractory (r/r) LBCL.[8] It was then subsequently extended to patients receiving CAR-T therapy for r/r MCL and multiple myeloma.[17,45] Calculated prior to lymphodepletion (day −5), the score incorporates both factors that relate to the baseline inflammatory state (e.g., C-reactive protein [CRP], ferritin) and the patient's hematopoietic reserve (e.g., hemoglobin, absolute neutrophil count [ANC], platelet count) (Figure 3). High-risk patients (score ≥2) exhibited increased rates of severe

infection (especially bacterial infections), higher non-relapse mortality, and inferior treatment outcomes compared to their low-risk counterparts (score 0-1).[11,45,46] We posit that the score may be used to restrict antibacterial prophylaxis and prophylactic G-CSF support to patients with a high-risk profile, as HT^{high} patients are more likely to benefit from these supportive measures because of their significantly higher rate of febrile neutropenia and infections.[11,26,45,47] On the other hand, HT^{low} patients may be suitable for avoidance of anti-infectives (i.e., fluoroquinolones, anti-mold agents), which may be beneficial due to the important role of an intact gut microbiome in the context of CAR-T therapy.[48,49] In addition, longitudinal measurements of serum procalcitonin (PCT) may be used to help rule out infections in the context of CRS (e.g., HT^{low} patients with non-elevated PCT at time of first fever).[46,50] Finally, the score may be useful to identify patients who require more extensive baseline diagnostic evaluations (e.g., pre-CAR-T BM biopsy). Prospective or retrospective data supporting or refuting these strategies should be generated. Limitations of the score relate to the lower specificity and positive predictive value and the fact that it has not been validated for use in BCP-ALL, follicular lymphoma, and pediatric patients (especially following relapse after hematopoietic stem cell transplantation).

Pathophysiology of ICAHT

The CAR-HEMATOTOX score underlines the importance of baseline hematopoietic function and systemic inflammation as risks for hematological toxicity. Baseline cytopenias likely reflect underlying impairment of the hematopoietic stem and progenitor cell (HSPC) compartment as a result of prior cytotoxic therapies.[51] They are also more frequently observed in cases of disease infiltration of the bone marrow, which represents an independent risk factor for hematotoxicity due to local inflammatory stressors and effects on HSPCs. In line with this observation, patients with prolonged cytopenias following BCMA-targeting CAR-T were more likely to display increased concentrations of CAR T-cells in the marrow post-infusion.[52] The high degree of systemic inflammation and secondary inflammatory insults that are stimulated by CAR-T infusion play a relevant pathophysiologic role, with several reports linking high-grade CRS and the associated inflammatory markers to prolonged cytopenias.[28,53] This may in part explain the more extensive hematotoxicity observed with the CD28z-endodomain harboring CAR-T products, although lymphodepletion dosing may also contribute.[5] In what manner the presence of preexisting clonal hematopoiesis of indeterminate potential (CHiP) may contribute to an underlying inflammatory state and subsequent development of prolonged cytopenias remains to be explored.[54,55]

Oligoclonal CAR-T-cell expansion and T-cell receptor restriction have been observed on the single-cell level in patients with protracted BM aplasia, together with an inflammatory micromilieu reminiscent of acquired aplastic anemia.[56] Strati et al employed single-cell RNA sequencing of bone marrow from patients with prolonged cytopenia to demonstrate that clonally expanded *CXCR1*^{hi}, *IFN-γ* expressing cytotoxic T cells were associated with hematopoietic stem cells (HSCs) that express IFN-γ response signatures.[57] This is consistent with data that IFN-γ can impair self-renewal and skew HSC differentiation.[58,59] Most importantly, these results expose potential therapeutic vulnerabilities, as IFN signaling can be targeted using IFN-neutralizing antibodies (e.g., emapalumab) or TPO-RA like eltrombopag.

Coagulopathy and hypofibrinogenemia

Patients undergoing CAR-T cell therapy are at risk for a spectrum of coagulopathies, from asymptomatic laboratory abnormalities to disseminated intravascular coagulation (DIC). Petechiae and ecchymosis are the most common manifestations of these coagulopathies. We discuss hemorrhage and bleeding complications, which are infrequent but potentially life-threatening, in a later section. Although coagulation abnormalities have been associated with poor progression-free survival (PFS), these reports

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 High: ≥2			

Low risk (HT 0-1) | High risk (HT 2-7)

Risk profile	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

Figure 3. Using the CAR-HEMATOTOX score for risk-adapted toxicity management. Reproduced with permission from Rejeski et al., *Blood* 2023.[9]

are severely limited in their interpretability given their correlations to CRS and ICANS and other inflammatory markers such as CRP and ferritin, which are known to be higher in the face of an immunosuppressive tumor microenvironment and elevation of suppressive myeloid cells in the tumor and periphery.[60,61]

The common toxicities of CAR-T, CRS and ICANS, are associated with a systemic inflammatory response and endothelial breakdown, respectively, both of which are likely contributors to the pathogenesis of consumptive coagulopathy and DIC. In a trial of primarily adult ALL patients treated with CAR-T, increased IL-6 and severe CRS corresponded to laboratory-defined coagulopathies, including D-dimer elevation, increased fibrin degradation products, and activated partial thromboplastin time (aPTT) elongation, while treatment of CRS aligned with their resolution.[62] Elevations of platelet endothelial cell adhesion molecule-1 (PECAM-1) and tissue factor (TF) were also seen, consistent with a disruption of endothelial integrity in the setting of CRS and ICANS.[62] The incidence of severe CRS has decreased with intervention using tocilizumab and corticosteroids at earlier grades, and the impact of these interventions on the incidence of coagulation abnormalities remains unclear.[1,63]

The frequency and degree of coagulation testing is not standardized across CAR-T trials or in real-world settings. With frequent evaluation, over 50% of patients may be discovered to have coagulation abnormalities within the first month after receiving CAR-T. Prothrombin and thrombin time prolongation, aPTT, and D-dimer elevation typically peak within the first 6-9 days, while fibrinogen nadir may be slightly later at 12-14 days.[60,64] Several attempts have been made to apply standardized DIC criteria scores to laboratory results in CAR-T patients; however, an association with bleeding has not been seen.[62,64] For example, Johnsrud et al applied the International Society on Thrombosis and Hemostasis DIC criteria to LBCL CAR-T-treated patients and found high rates of DIC yet no correlation with bleeding events. They postulated that thrombocytopenia after CAR-T is more likely related to lymphodepleting chemotherapy or immune-mediated suppression rather than platelet consumption seen in classical DIC.[65] While evaluation of laboratory tests of coagulation may help aid decision-making and management in the CAR-T patient, the diagnostic utility of DIC-scoring algorithms remains uncertain, and more evaluation is needed. There is wide variation across practitioners and institutions on which tests, including D-dimer, fibrin degradation products, thrombin time, prothrombin time, aPTT, and fibrinogen, are checked and when. Furthermore, there is little data to indicate that utilization of these parameters to guide interventions improves outcomes. Our general practice in adult patients is to evaluate these parameters at baseline and again after CAR-T only when a patient experiences severe or refractory CRS or bleeding events.

Fibrinogen concentrate or cryoprecipitate can effectively correct hypofibrinogenemia in the setting of CAR-T therapy. In pediatric and adolescent/young adult ALL patients, severe CRS and consumptive coagulopathies are more commonly observed than in the adult population. Tisagenlecleucel investigators summarized coagulopathies seen in BCP-ALL patients and developed practical guidelines for monitoring and managing coagulopathies, particularly fibrinogen replacement. Despite the relatively common occurrence of hypofinrinogenemia, severe bleeding events were relatively rare, occurring in 1.4% of cases. Buechner and colleagues recommend intervening with cryoprecipitate or fibrinogen only when grade 3-4 CRS occurs and fibrinogen levels are very low at <1 g/L, replacing to >1.5 g/L until CRS resolves to <G3.[66] In a series of adult LBCL patients undergoing CAR-T, severe hypofibrinogenemia was detected in 6% of patients between day 0 and 100, and it was not associated with bleeding events. However, the fibrinogen level was only checked in 20% of patients and was at the discretion of the treating physician, thus preventing extrapolation of incidence or bleeding risk.[64] Although grade 3-4 CRS in adult patients is rare, and the incidence of concomitant hypofibrinogenemia is uncertain, practitioner awareness of these guidelines is important when the situation may arise.[66]

Bleeding and thrombosis after CAR-T

While severe bleeding events are rare, the risk of hemorrhage after CAR-T may be underappreciated. In pivotal trials of CAR-T cell therapy, severe bleeding events were rare. Bleeding events are most likely to occur within the first 30 days after CAR-T.[65] In one retrospective series, bleeding events were seen in 11% of LBCL CAR-T patients, a minority of which were severe, and they were seen more frequently in the elderly or those with prior bleeding events, those with baseline and concomitant thrombocytopenia, and patients with ICANS consistent with its known association with endothelial dysfunction.[65] Reports of cerebral bleeding events, particularly in the setting of CRS and ICANS, may be attributed to this endothelial dysfunction.[29]

The incidence of thrombotic events after CAR-T are variably seen in 2-11% of cases, having associations with D-dimer elevation and ICANS.[67] In contrast to bleeding events, thrombosis events are more likely to occur up to day +90. Importantly, anticoagulation medications, either as prophylactic or treatment, have not been associated with bleeding events. In a series of 148 LBCL CAR-T patients, 11% of patients experienced a thrombotic event, and these were safely managed with anticoagulation. In this series, routine prophylaxis was not employed. However, therapeutic anticoagulation after thrombotic events was not associated with bleeding.[64] A more recent series, also in LBCL patients, reported only a 2% rate of thrombotic events when prophylactic anticoagulation was used in most patients.[68] Taken together, these data suggest that patients at moderate to high risk of thrombosis or with a prior history of thrombosis requiring anticoagulation can safely receive prophylactic or therapeutic anticoagulation, respectively, after CAR-T with cessation at platelet counts <50,000/μL, and such intervention may reduce the incidence of thrombotic events after CAR-T.

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)

Secondary hemophagocytic lymphohistiocytosis can occur after CAR-T, typically with hemaphaogocytosis and other HLH-like features occurring after the resolution of acute CRS and, more commonly, with CD22-directed CAR-T.[69,70] Classical definitions of secondary HLH have diagnostic criteria that overlap with the common features of CRS, which itself is associated with the HLH adjacent macrophage activation syndrome. A need to further delineate CRS from this discrete CAR-T-related HLH entity led one panel of experts on HLH and cell therapy to define and name

it IEC-HS, as well as create a severity grading algorithm and management recommendations.[71]

According to the American Society for Transplantation and Cellular Therapy (ASTCT) expert panel, IEC-HS refers to "the development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis."[71] A requirement for diagnosing the syndrome is an elevated and/or rapidly rising serum ferritin. As biphasic CRS can occur, classical recurrence of CRS as an alternative diagnosis should be considered.

Early recognition is critical, and alternative etiologies such as malignancy progression or infection should be ruled out. Initial therapy with the IL-1 receptor antagonist anakinra, with or without corticosteroids, is suggested. Following 48 hours for response assessment, additional agents such as the JAK1/2 inhibitor ruxolitinib, the anti-IFN-γ antibody emapalumab, or low-dose etoposide chemotherapy could be considered depending on the patient's trajectory.[71]

Tumor lysis syndrome

Although tumor lysis syndrome (TLS) following CAR-T cell therapy can occur, clinically significant manifestations of the syndrome are unusual in ALL, lymphoma, or myeloma patients and potentially more common in chronic lymphocytic leukemia. As with coagulopathies, evaluation of electrolyte abnormalities may suggest tumor lysis; however, clinical manifestations such as creatinine elevation may have multifactorial etiologies, including hypotension, in the setting of CRS or nephrotoxicity from concomitant co-medications.[72] In patients with a history of TLS or those with high circulating tumor burden, allopurinol prophylaxis can be considered.

Conclusion

Recognition of noncanonical hematologic toxicities after CAR-T cell therapy is critical for the practitioner. The development of uniform diagnostic criteria and severity grading systems will inform reporting on their incidence and help investigators elucidate their mechanisms. Significant strides have been made to define ICAHT and IEC-HS as distinct toxicity categories of CAR T-cell therapy. This now sets the stage for evaluating severity-based management recommendations and studying the applicability of these grading systems across disease entities and indications, including for solid tumors, pediatric patients, bispecific antibody therapies, and novel CAR constructs. Future studies will need to examine the potential of prophylactic stem cell collection in patients at ultra high risk for ICAHT, although this may incur an additional logistic burden and increase costs. More work must be done to quantify and define monitoring and management strategies for coagulopathies, bleeding and thrombosis events, and tumor lysis after CAR-T. Emerging areas of interest relate to the association between CHiP and the development of prolonged cytopenias, CRS, ICANS, and therapy-related myeloid neoplasms. Innovative single-cell and multi-omic approaches and modern imaging techniques may help to uncover the still vexing pathophysiology of ICAHT and IEC-HS. Finally, these efforts must ideally leverage the power of multicenter collaborations that span multiple CAR-T centers and countries to optimize resources and leverage diverse patient populations.

Authorship

*Kai Rejeski and Marion Subklewe contributed equally to this article.

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Kai Rejeski: Kite/Gilead: Research Funding, Consultancy, Honoraria and travel support; Novartis: Honoraria; BMS/Celgene: Consultancy, Honoraria; Pierre-Fabre: travel support.
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Off-label drug use

Kai Rejeski: nothing to disclose.
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