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Immune Effector Cell-Associated Hematotoxicity (ICAHT): EHA/EBMT Consensus Grading and Best Practice Recommendations

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Abstract:
Hematological toxicity represents the most common adverse event following chimeric antigen receptor (CAR) T-cell therapy. Cytopenias can be profound, long-lasting, and can predispose for severe infectious complications. In a recent worldwide survey, we demonstrated that there remains considerable heterogeneity in regards to current practice patterns. Here, we sought to build consensus on the grading and management of Immune Effector Cell Associated Hemato-Toxicity (ICAHT) following CAR-T therapy. For this purpose, a joint effort between the European society for Blood and Marrow Transplantation (EBMT) and the European Hematology Association (EHA) involved an international panel of 36 CAR-T experts who met in a series of virtual conferences, culminating in a 2-day meeting in Lille, France. On the basis of these deliberations, best practice recommendations were developed. For the grading of ICAHT, a classification system based on depth and duration of neutropenia was developed for early (day 0-30) and late cytopenia (after day +30). Detailed recommendations on risk factors, available pre-infusion scoring systems (e.g. CAR-HEMATOTOX score), and diagnostic work-up are provided. A further section focuses on identifying hemophagocytosis in the context of severe hematotoxicity. Finally, we review current evidence and provide consensus recommendations for the management of ICAHT, including growth factor support, anti-infectious prophylaxis, transfusions, autologous hematopoietic cell boost, and allogeneic hematopoietic cell transplantation. In conclusion, we propose ICAHT as a novel toxicity category following immune effector cell therapy, provide a framework for its grading, review literature on risk factors, and outline expert recommendations for the diagnostic work-up and short- and long-term management.

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Immune Effector Cell-Associated Hematotoxicity (ICAHT): EHA/EBMT Consensus Grading and Best Practice Recommendations

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Abstract

Hematological toxicity represents the most common adverse event following chimeric antigen receptor (CAR) T-cell therapy. Cytopenias can be profound, long-lasting, and can predispose for severe infectious complications. In a recent worldwide survey, we demonstrated that there remains considerable heterogeneity in regards to current practice patterns. Here, we sought to build consensus on the grading and management of Immune Effector Cell Associated Hemato-Toxicity (ICAHT) following CAR-T therapy. For this purpose, a joint effort between the European society for Blood and Marrow Transplantation (EBMT) and the European Hematology Association (EHA) involved an international panel of 36 CAR-T experts who met in a series of virtual conferences, culminating in a 2-day meeting in Lille, France. On the basis of these deliberations, best practice recommendations were developed. For the grading of ICAHT, a classification system based on depth and duration of neutropenia was developed for early (day 0-30) and late cytopenia (after day +30). Detailed recommendations on risk factors, available pre-infusion scoring systems (e.g. CAR-HEMATOTOX score), and diagnostic work-up are provided. A further section focuses on identifying hemophagocytosis in the context of severe hematotoxicity. Finally, we review current evidence and provide consensus recommendations for the management of ICAHT, including growth factor support, anti-infectious prophylaxis, transfusions, autologous hematopoietic cell boost, and allogeneic hematopoietic cell transplantation. In conclusion, we propose ICAHT as a novel toxicity category following immune effector cell therapy, provide a framework for its grading, review literature on risk factors, and outline expert recommendations for the diagnostic work-up and short- and long-term management.

Introduction and state-of-the-art

The last decade has firmly established chimeric antigen receptor (CAR) T-cell therapy as a practice-changing immunotherapy platform for an increasing number of refractory B-cell malignancies.[1-7] While durable remissions can be achieved, this comes with the caveat of a unique spectrum of side effects ranging from Cytokine Release Syndrome (CRS), to Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS), and Immune Effector Cell Associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS).[8-11] Real-world evidence has underlined the growing importance of hematological toxicity as the most frequent Common Terminology Criteria for Adverse Events (CTCAE) grade ≥3 adverse event following CAR T-cell therapy.[12-14] Similarly high rates of cytopenias have been reported for other T-cell based immunotherapies such as bispecific antibodies.[15-19] Notably, profound and often long-lasting cytopenias can add to the immunosuppression conferred by B-cell aplasia and consecutive hypogammaglobulinemia.[20] Importantly, severe infections are a major driver of both morbidity and non-relapse mortality (NRM) following CAR T-cell therapies.[21-23]

Hematological side effects have been described after CAR T-cell therapy regardless of the target antigen (e.g., CD19 vs. CD22 vs. BCMA) and across various disease entities (e.g., LBCL, BCP-ALL, MCL, MM, FL).[3-5,24-29] Several features underline the unique nature of CAR-T related hematotoxicity. First, cytopenias can persist long after the resolution of clinical CRS, and have been reported as long as months to years following CAR T-cell infuson.[30] Hematopoietic count recovery often follows a biphasic trajectory, with intermittent recovery followed by second, or multiple, dips.[12,13] Second, patients can develop very severe bone marrow (BM) aplasia that is often refractory to therapeutic measures such as growth factor support.[13,31,32] Finally, the underlying pathophysiology remains to be elucidated, although recent evidence points towards the importance of both baseline hematopoietic reserve and the systemic inflammatory state of the host.[13] Moreover, the inflammatory stress conferred by severe CRS and the associated alterations in cytokine patterns can exert myelosuppressive effects.[33-35]

In a recent international survey led by EHA and EBMT, we identified a high degree of heterogeneity both in regards to the grading and management of cytopenias.[36] Current grading systems such as the CTCAE describe cytopenias predominantly in quantitative terms by assigning severity grades according to the depth of cytopenia. However, they are difficult to apply in daily practice and fail to capture the distinct nature of post-CAR-T hematopoietic reconstitution, such as the biphasic and/or delayed course. Furthermore, the cumulative risk of secondary complications (e.g., infections, bleeding) primarily increases with the respective duration of observed cytopenia.[22,37] Classification systems that were developed for cytopenia following classic cytotoxic chemotherapies may not apply to patients receiving novel T-cell based immunotherapies. To accommodate these unique features of hematological side effects in adult patients receiving such therapies, we herein introduce the concept of Immune Effector Cell Associated Hemato-Toxicity, or ICAHT. Based on a novel framework for grading, we outline expert recommendations for its diagnostic work-up and management.

Methodology

This workshop is based on the EBMT PH & G committee method.[38] In September 2022, KR and MS proposed to set up a workshop to issue European recommendations regarding the grading and management of ICAHT, particularly following autologous CAR T-cell therapy. As a first step, an international survey on current practices at >50 global CAR-T centers was sent out and results were analyzed.[36] Experts from different countries and belonging to EBMT and EHA were subsequently invited to join the workshop. As a second step, several teleconferences took place to discuss and advance the first draft. Along with the results of the international survey, a comprehensive literature review was carried out by the workshop participants within each subgroup, which served as the basis for the discussions. The third step consisted of a two-day face-to-face meeting which took place in Lille, France on March 2nd and 3rd, 2023.

These recommendations are intended to be general in scope and applicable to all diseases and types of autologous CAR T-cell therapies or other T-cell based immunotherapies (e.g., bispecific antibody constructs) adopted as standard clinical practice. They are intended to reflect current best practices in this new and rapidly evolving field and aim to help clinicians and other healthcare professionals in providing consistent, high-quality patient care. These recommendations were created due to the growing number of autologous CAR T-cell therapies currently available outside clinical trials for the treatment of hematological malignancies. Given the lack of high-quality evidence from randomized trials in this area (expected Evidence Levels 3-5, Oxford Centre for Evidence Based Medicine), the decision was made not to grade these recommendations. They therefore represent the consensus point of view of the authors. When administering CAR T-cell therapies within clinical trials, physicians are advised to follow respective trial protocols.

Consensus recommendations

1. ICAHT Grading

On the basis of the results of the international survey on behalf of EHA and EBMT, the expert panel defined early ICAHT as cytopenia occurring during the first 30 days after CAR T-cell infusion. Conversely, late ICAHT was classified as cytopenia observed beyond day +30. The expert panel resolved that the main clinical action points of post-CAR-T cytopenias concerned profound and/or prolonged neutropenia, and that isolated thrombocytopenia or anemia represent rare occurrences. Concomitantly, a grading system based on neutropenia was pursued. For early ICAHT (day 0-30), a grading system based on both depth and duration of neutropenia was defined due to the associated clinical sequelae (**Table 1**, top). Late ICAHT was graded based on the elapsed time from CAR T-cell infusion (e.g., occurring after day +30) with the severity (grade I-IV) defined by the depth of neutropenia (**Table 1**, bottom). For anemia and thrombocytopenia, the expert panel refers to existing grading systems and recommends that institutional guidelines should be followed, as further outlined in **Section 6** and **Table 4** (see *transfusions*).

2. Risk factors for developing post-CAR-T cytopenias

The overall incidence of hematological toxicity in the key registrational trials for CAR T-cell products endorsed by the European Medicines Agency (EMA) are outlined in the **Supplemental Table 1**. Furthermore, we performed an extensive literature review of prominent real-world studies with a specific focus on correlative studies and potential risk factors (**Supplemental Table 2**). Overall, a plethora of factors contribute to the development of cytopenias after CAR-T, some of which remain incompletely understood. Broadly, they relate to the underlying disease and its previous treatments, baseline risk factors (e.g., hematopoietic reserve, BM infiltration, systemic inflammation), as well as CAR-T product features and CRS-related inflammatory patterns (summarized in **Table 2** and the **Supplementary Text**).[12,13,23,30,33,34,39-56]

3. What scoring systems to use

Based on several of the risk factors delineated above, the CAR-HEMATOTOX score was developed to identify patients at high risk for prolonged neutropenia, and especially the development of the aplastic phenotype of neutrophil recovery.[13] An online calculator can be found on the website of the German Lymphoma Alliance (GLA): https://www.german-lymphoma-alliance.de/Scores.html). The score incorporates factors related to hematopoietic reserve (absolute neutrophil count [ANC], hemoglobin, platelet count) and baseline inflammatory state (CRP, ferritin) and was validated for a primary endpoint of severe neutropenia (ANC <500/µL) lasting longer than 14 days during the first 60 days after CAR-T infusion. Importantly, the CAR-HEMATOTOX score is determined prior to lymphodepleting chemotherapy and thus enables early risk-stratification into a high vs. low risk of developing severe hematotoxicity after CAR T-cell treatment (**Figure 1**). In subsequent studies, the score also identified patients at risk for severe infections and poor treatment outcomes across multiple disease entities (e.g., LBCL, MCL, MM).[22,42-44,57] However, it is important to note that the score remains to be validated prospectively and for adult and pediatric BCP-ALL patients. Furthermore, the test characteristics (high sensitivity, lower specificity) indicate a lower positive predictive value, meaning that not all patients deemed high-risk will develop severe hematotoxicity. Conversely, the high negative predictive value suggests that the score is particularly helpful in ruling out patients at risk for severe hematotoxicity.

4. Assessment and diagnostic work-up of ICAHT

In patients with a high-risk profile for developing ICAHT (**Table 2, Figure 1**), baseline BM studies (prior to apheresis or lymphodepletion) should be considered to risk-stratify patients for hematological toxicity and identify underlying marrow infiltration as a pertinent risk factor. Cryopreservation of the BM aspirate and/or peripheral blood mononuclear cells (PBMCs) is optional, but may provide useful information in case the patient develops secondary BM failure (e.g., presence of CHiP clone).

In case of cytopenia that persists beyond the expected reconstitution of lymphodepleting chemotherapy (typically following week 2-3 after CAR-T infusion), the first step in the work-up comprises defining the differential diagnosis, which can include drug-induced cytopenia, vitamin deficiencies, infectious causes, sustained inflammatory stressors, relapse and/or active BM disease. The expert panel recommends performing an incremental diagnostic-work-up, with an initial tier 1 assessment comprising standard diagnostic tests that should be performed in all cases of severe, or grade ≥III, ICAHT (**Figure 2**). In case the tier 1 results are inconclusive and cytopenias persist and/or are G-CSF refractory (absence of count recovery despite ≥5 days of G-CSF support), a subsequent tier 2 diagnostic work-up can be pursued. Importantly, this includes extended viral studies, as well as BM aspiration and biopsy. The expert panel would reserve cytogenetics and next-generation sequencing to rule out an underlying myeloid malignancy to either cases of profound, long-lasting marrow aplasia (e.g., no count recovery above an ANC ≥500/µL by day +30, pancytopenia), or new-onset pancytopenia that is refractory to therapeutic measures late after CAR-T infusion.

5. Hemophagocytosis associated with severe hematotoxicity after CAR T-cell therapy

Hemophagocytic lymphohistiocytosis (HLH) represents a hyper-inflammatory condition resulting from abnormal immune activation, which is associated with high fever, hyperferritinemia, prolonged cytopenia and eventually multi-organ failure. HLH remains a diagnostic quandary as unique biomarkers are still lacking and/or not readily available. In the context of CAR T-cell therapy, the incidence of HLH-like symptoms ranges from 1% to 3.4%.[10,58] Two entities, CRS/MAS and IEC-HS, can be distinguished according to time of onset and presence of concomitant CRS/ICANS symptoms.[29,59-61] In patients with severe ICAHT that present with aplastic neutrophil recovery and rising serum ferritin, the diagnosis of HLH should be considered, as both can present with profound immune dysregulation and increased IFN signaling.[42,54] A comprehensive work-up is recommended in order to identify additional abnormalities such as new-onset hepatosplenomegaly, hypertriglyceridemia, coagulopathy and hypofibrinogenemia, as well as hemophagocytosis features on BM biopsy or in other tissues (**Fig. 2**). Existing scoring systems that can guide the diagnosis of HLH in the context of severe ICAHT include HLH-2004 criteria, the H-score, and the OHI index.[62-64] Additionally, **Table S3** outlines the MD Anderson criteria[58], EBMT/EHA/JACIE recommendations[59] and IEC-HS criteria[60], which were deemed more specific to CAR-T therapy by the expert panel. In patients in whom ICAHT manifests in the form of HLH, anti-inflammatory measures should be promptly initiated to mitigate cytokine storm and its clinical sequelae. Patients should be treated with anakinra, a recombinant humanized IL-1 receptor antagonist, in combination with high-dose corticosteroids (**Figure S1**). In refractory cases, ruxolitinib, cytokine adsorption, and emapalumab (IFN-γ inhibitor) can be considered, albeit data remains scarce.[65-67]

6. Management of cytopenias

The management of ICAHT can broadly be separated into an initial phase which addresses the (expected) early cytopenias and aims to mitigate the risk of infections and/other complications, as well as a later phase that is initiated in case of persistent and/or therapy-refractory cytopenias. An overview of the expert recommendations for early ICAHT management if provided in **Table 3**.

Transfusions

Due to the frequent nature of severe anemia and thrombocytopenia after CAR-T therapy, transfusions are an essential part of supportive care and include either packed red blood cell concentrates (pRBCs) or platelet concentrates (PCs). Transfusion-associated GvHD (ta-GvHD) is a rare complication of transfusion wherein viable donor T lymphocytes in cellular blood products mount an immune response against the recipient.[68] Considering the high mortality rate (>90%), prevention of ta-GvHD is recommended, though there is no internationally agreed upon consensus on the duration of the use of irradiated blood products across cellular therapies. In the setting of HCT, standard practice is to use irradiated blood for (1) at least 2 weeks prior to stem cell collection until at least 3 months after auto-HCT, and (2) starting with conditioning at the latest until at least 6 months after allo-HCT, or until immune reconstitution.[69] In the context of CAR-T therapy, the expert panel recommended the irradiation of blood products from 7 days prior to leukapheresis until at least 90 days post-CAR-T infusion unless conditioning, disease or previous treatment determine indefinite duration (**Table 3**). Of note, the use of the purine analogue fludarabine as a component of lymphodepletion prior to CAR-T infusion may impact local guidance for irradiated blood products.[69] Given its relative rarity, we recommend reporting cases of ta-GVHD following CAR-T to regulatory authorities.

Growth factor support

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF is typically elevated in CAR-T patients with CRS and ICANS. The use of GM-CSF as a growth factor for patients with low blood counts should be avoided as it may promote inflammatory toxicity and induce neuroinflammation following CAR-T therapy.[70,71]

Granulocyte colony-stimulating factor (G-CSF)

Due to the concerns for the use of GM-CSF and the hypothesized, but largely unknown risks of exacerbating toxicities, early guidance suggested generally deferring G-CSF until resolution of acute CAR T-cell related immunotoxicity (typically week 3). However, several recent reports question this as a general rule and point towards an acceptable safety profile for the early use of G-CSF, with no increase of high-grade (≥3°) CRS/ICANS.[72-76] In the largest retrospective analysis by Miller and colleagues (n=197), prophylactic G-CSF *before* CAR-T (mostly pegylated G-CSF) was associated with faster neutrophil recovery, comparable treatment outcomes, and similar rates of severe ICANS.[75] While prophylactic G-CSF was associated with a higher rate of grade ≥2 CRS, this observation did not extend to the clinically relevant grade ≥3 CRS. In a subgroup analysis, the authors found that G-CSF did not worsen severity of CRS in patients who *already* present with low-grade (1°) toxicity. In a further study by Lievin et al, early G-CSF administration (from day +2) in neutropenic patients was associated with a reduced risk of febrile neutropenia without increasing the risk of severe CRS or ICANS.[74] Notably, G-CSF was also safe in maintaining CAR T-cell expansion kinetics and anti-lymphoma activity, without any deleterious impact on the quality of response and outcomes.[73,74] Appraising the above evidence and weighing the benefits and risks, early G-CSF administration on day +2 can be considered in high-risk patients to shorten the length of expected severe neutropenia (see **Table 2** and **Figure 1**). Therapeutic G-CSF in case of prolonged severe neutropenia (ANC <500/µL) can also be considered, and can be of diagnostic benefit for identifying the aplastic neutrophil recovery phenotype[13,32], which is often G-CSF unresponsive. The large majority of CAR-T patients (>80%) ultimately respond to growth factor support with count recovery.[32,34] However, recurrent neutrophil dips (biphasic course) can necessitate intermittent application of therapeutic G-CSF (**Figure 3**). Finally, a uniform consensus was reached on the necessity of *prospective*, and ideally multicenter, clinical trials that evaluate the safety and optimal treatment protocol for G-CSF (prophylactic vs. early / pegylated vs. non-pegylated) in the context of CAR-T therapy and across disease entities (B-ALL vs. B-NHL vs. MM).

Thrombopoietin (TPO) agonists

TPO agonists (e.g., eltrombopag, romiplostim) are considered primarily in patients with prolonged and late thrombocytopenia, with the thrombocytopenic nadir typically occurring in the 2nd month after CAR-T therapy.[12,13] Data supporting the use of TPO agonists in the CAR-T setting are extremely limited and are restricted to a few case series from single centers with limited patient numbers.[77-79] In these limited reports, improvement in platelets and also hemoglobin and ANC was noted, with some patients becoming transfusion independent both for platelets and pRBCs similar to improvement in hematopoiesis observed with TPO agonist use in cases of acquired BM failure.[80,81] Due to the limited available data, the expert panel advises that the use of TPO agonists should parallel the practice for HCT.[82] They can also be utilized in G-CSF refractory cases of ICAHT (**Figure 3**).

Infection prophylaxis

Regarding the administration of anti-infectious prophylaxis during cytopenia, the expert panel broadly recommends adherence to the general EHA/EBMT/JACIE guidelines for patients receiving CAR T-cell therapy.[59] The following specific recommendations were issued (**Table 3**):

- Adherence to current EHA/EBMT guidelines regarding anti-viral and anti-pneumocystis pneumonia (PCP) prophylaxis, as well as intravenous immunoglobulin (IVIG) substitution for post-CAR-T hypogammaglobulinemia.[59]
- The expert panel does not recommend the use of a neutropenic diet to reduce the risk of infection in neutropenic CAR-T patients.[83-85]

- **Antibacterial prophylaxis**: the panel proposes a risk-adapted strategy based on the patient-individual risk profile for infections including the expected incidence rate of protracted, profound neutropenia (ANC <100/µL for ≥7 days), in line with the consensus American Society of Clinical Oncology (ASCO)/ Infectious Diseases Society of America (IDSA) recommendations for adult cancer patients.[86] Antibacterial prophylaxis with a fluoroquinolone (e.g. levofloxacin, ciprofloxacin) is not recommended in patients who are at a low risk of severe (grade ≥III) ICAHT (**Table 1**, **Table 3**) and should be avoided due to fluoroquinolone-specific side effects, the potential emergence of resistant strains, and selection for *C. difficile* and *enterococci*.[37,87-90] Furthermore, recent publications have demonstrated that antibiotic exposure prior to CAR T-cell therapy reduces microbiome diversity and is associated with inferior outcomes, potentially due to the multifunctional and immunomodulatory role of the gut microbiome.[91-94] On the other hand, antibacterial prophylaxis can be considered in high-risk patients once the ANC falls below <500/µL to mitigate the risk of severe infections. The CAR-HEMATOTOX score may be useful for guidance and identification of high-risk candidates.[13] In a large retrospective analysis of LBCL patients receiving CD19 CAR-T, a significant reduction of severe bacterial infections with fluoroquinolone prophylaxis was observed in CAR-HEMATOTOX^{high} but not CAR-HEMATOTOX^{low} patients, supporting a risk-adapted approach. Importantly, the panel recommends adherence to institutional guidelines that take into account local epidemiology and resistance patterns. In this context, monitoring for multi-drug resistant gram-negative bacteria (MDR GNB) colonization (i.e., active surveillance through rectal swab culture) may be useful both for baseline risk assessment and during prolonged neutropenia.
- **Antifungal prophylaxis:** To reduce the risk of invasive fungal disease (IFD), anti-mold prophylaxis (e.g., micafungin or posaconazole) can be considered in patients at high risk for severe ICAHT (grade ≥III) once the ANC falls below <500/µL (**Table 3**). Additional risk factors to consider are prior allo-HCT, prior invasive aspergillosis and receipt of corticosteroids (either long-term ≥72h or high-dose, e.g., greater than 10 mg of dexamethasone or equivalent). The low overall incidence rate for IFD in the context of CAR-T should be taken into account[95], although fungal infections represent a frequent cause of fatal infectious complications.[22,96] Systemic primary antifungal prophylaxis should

be continued until stable count recovery (ANC >500/µL over 3 days) and discontinuation of steroids for CRS/ICANS management.

Hematopoietic cell boost

Patients who are unresponsive and/or refractory to G-CSF beyond day +14 after CAR-T infusion represent a clinically challenging subgroup of patients at high risk for severe and even fatal infectious complications. While the evidence remains limited, TPO agonists can be offered in this setting, especially in cases of associated thrombocytopenia.[79] In cases of severe ICAHT in which an inflammatory stressor is deemed contributory (severe CRS/ICANS, CRS/MAS), anti-inflammatory strategies such as pulse-dose corticosteroids and/or anti-cytokine therapies (e.g., tocilizumab, anakinra) should be used. A promising strategy pertains to the use of cryopreserved autologous or allogeneic $CD34^+$ hematopoietic cells from prior collection (either prior auto- or allo-HCT).[97-99] Three recent case series shed light on both the safety and clinical feasibility of this approach across a broad population of pediatric and adult patients (summarized in **Supplemental Table 4**). High rates of sustained neutrophil and platelet engraftment were noted across studies. While hematopoietic cell boost (HCB) has been successfully applied during active infection[100], clinicians should be aware of the possibility of immune reconstitution inflammatory syndrome (IRIS) in patients with prolonged bone marrow aplasia.[31] As the earlier application of an *available* HCB was associated with superior survival outcomes,[99] the expert panel recommends considering the application of a HCB without prior conditioning chemotherapy for grade ≥III ICAHT beyond day +14 if (1) a boost is readily available and (2) G-CSF refractoriness has been established. At the same time, the survey results highlighted that even when HCB were considered a viable treatment option in a patient with prior auto-HCT, they were often not available. While prophylactic collection in high-risk candidates has been proposed as a potential mitigating strategy, the panel cautioned that the collection process may add to the already high logistic burden of CAR T-cell therapy (e.g., coordination of apheresis slots and storage capacity), which could negatively impact vein-to-vein times in a state of high disease burden. Furthermore, the process could incur unnecessary collection- and storage-associated costs.[101,102] Ultimately, it was concluded that further research is needed to assess the number needed to treat for prophylactic stem cell collection.

Allogeneic hematopoietic cell transplantation

If the above options remain ineffective or elusive and grade IV ICAHT persists beyond day +30, the expert panel recommends initiating a donor search for a potential allo-HCT as a last resort (ultima ratio). In such cases of life-threatening ICAHT, the benefit and risks of allo-HCT need to be carefully weighed and aligned with the patient's goals-of-care. Furthermore, the possibility of spontaneous count recovery needs to seriously be considered.[34,103,104] Accordingly, the expert panel suggested that the ultimate trigger for allo-HCT needs to be discussed on a case-by-case basis. Month 3-6 post CAR-T infusion was deemed a reasonable time frame to balance both the risk of infection and possibility of spontaneous count recovery. Once the decision for allo-HCT has been made, details regarding donor selection, conditioning regimens and immunosuppression have to be discussed. Experience and evidence are very limited and only general considerations can be reviewed here. As for every allo-HCT, the same basic principles should apply keeping in mind that the primary indication is severe and persistent cytopenia although basically all patients currently receive commercially available CAR-T cells to treat malignant lymphoid disorders. Most importantly, salvage allo-HCT is also capable to provide tumor control through the conditioning regimen and graft-versus-tumor effects and current standard procedures will most likely lead to eradication of CAR-T cells at the latest when full donor chimerism has been established. Therefore, remission status must be determined prior to allo-HCT and may guide the choice of conditioning regimen and the taper of immunosuppression. As usual, performance status, comorbidities, prior therapies and expected anti-tumor activity should be carefully considered when discussing the transplantation modalities, donor choice and selection.

7. Conclusions and Outlook

Much progress has been made in the last years in defining hematological toxicity as a distinct toxicity entity of CAR T-cell therapy. While the underlying pathophysiology remains incompletely understood, growing evidence points towards critical interactions between host hematopoiesis and CAR T-cell function and efficacy. By defining ICAHT and delineating a specific grading system, we herein provide a nomenclature that enables cross-trial comparisons and invites severity-based management strategies.

In this international consensus guidelines document, we have proposed a structured approach to diagnosis, grading/staging and clinical management of ICAHT. This endeavor has also set the stage for areas of future development that will require collaboration between various European and non-European stakeholders involved in CAR T-cell therapy. Structured sample collection across multiple centers represents the basis for translational projects that delineate the underlying mechanisms of ICAHT by leveraging novel technologies such as multi-omics and single-cell approaches. One area of particular interest lies in identifying early determinants of ICAHT by studying the peripheral blood immune contexture and/or the local BM microenvironment from pre-CAR-T samples. Furthermore, large retrospective real-world analyses may shed light on some of the differences in the clinical management of ICAHT that were identified by the EHA/EBMT survey. Residual questions relate to the optimal timing of G-CSF initiation as well as the optimal protocol to employ (e.g., prophylactic vs. early G-CSF). The question of prophylactic collection of CD34+ hematopoietic cells in high-risk candidates and the optimal trigger time point for both HCB and allo-HCT represent unresolved issues that warrant further systematic study. Ultimately, prospective clinical trials will be needed that determine the potential benefits and evidence-base of treatment strategies that mitigate ICAHT.

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Main Tables and Table Legends

Table 1: 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

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

	Risk Factors	Comments	References
Disease-related features	Underlying disease (ALL > B-NHL)	Evidence concerning the rate of cytopenias in multiple myeloma patients still emerging	Xia et al.[39]
	Disease burden at CAR-T infusion (progressive disease, high LDH)	Specially BM disease burden	Wudhikarn et al.[14] Logue et al.[103]
Prior therapies	Number of prior therapy lines	Associated with baseline hematopoietic function	Xia et al.[39]
	Prior hematopoietic stem cell transplantation (HSCT)		Fried et al.[105]
	Bridging Therapy		Roddie et al.[41]
Baseline Marrow Status	Bone marrow infiltration		Rejeski et al.[42] Brudno et al.[40]
	Pre-existing cytopenias	Particularly pre-existing thrombocytopenia	Rejeski et al.[13] Juluri et al.[33] Saini et al.[46]
	Clonal hematopoiesis of indeterminate potential (CHiP)?	Has been linked to increased inflammation, potential emerging risk factor	Miller et al.[47] Teipel et al.[86]
Baseline Inflammatory Status	Increased Serum CRP		Rejeski et al.[13]
	Increased Serum Ferritin		Rejeski et al.[13]
CAR-T Product and post-infusion risk factors	Co-stimulatory molecule (CD28>41BB)	May also reflect differences in lymphodepletion dosing (cyclophosphamide dosing)	Xia et al.[39]
	Type of construct (Tandem > single target)		Xia et al.[39]
	Severe CRS		Juluri et al.[33] Jain et al.[34]
	Sustained increased inflammatory markers		Juluri et al.[33]
	Oligoclonal T-cell expansion	In select patients; the success of auto-HCT boost argues against this as a general mechanism	Rejeski et al.[35]
	Active Infection	Mainly viral or in case of concomitant sepsis	Pascutti et al.[106]
	CRS/MAS or IEC-HS	Cytopenia as overlapping symptomology	Sandler et al.[10] Hines et al.[11] Porter et al.[107]

Table 3: Short-term management of cytopenias

	When	How	Precautions	Comments
Packed red bood cell (pRBC)/ Platelet transfusions	As per institutional standards, based on patient risk profile	As per institutional standards For pRBC: consider using 1 product per time to reduce iron overload[69]	Irradiation of blood products; Start 7 days prior to leukapheresis until at least 90 days post CAR-T	Due to the use of fludarabine
G-CSF	**Prophylactic G-CSF:** On day +2 in patients with a high-risk profile for ICAHT (e.g. high CAR-HEMATOTOX score and risk profile according to **Table 2**)	Based on individual risk profile: Consider early G-CSF administration (from day +2) as prophylaxis in high risk for ICAHT Dosing: 5 µg/kg once daily	In patients at low risk for ICAHT, G-CSF probably not necessary*	Reduced risk of febrile neutropenia (without increasing the risk of severe, or grade ≥3, CRS nor ICANS). No detrimental effect on CAR-T expansion kinetics or treatment outcomes[74,75]
	Therapeutic G-CSF: Severe neutropenia (ANC <500/µL) neutropenia with or without infectious complications	In case of prolonged neutropenia with/without infectious complications. Dosing: 5 µg/kg once daily, consider increasing dose in case of non-response		Patients with intermittent neutrophil recovery often rapidly respond to G-CSF stimulation, while aplastic patients are often G-CSF unresponsive
Antibacterial prophylaxis	In patients with a low risk for ICAHT, not recommended. In patients with a high-risk profile for ICAHT, prophylaxis may be considered once ANC <500/µL.	As per institutional standards (e.g. levofloxacin or ciprofloxacin).	Warning in case of colonization by MDR pathogens.	Look at local bacterial epidemiology. High local prevalence of MDR GNB might prevent the use of antibacterial prophylaxis
Anti-viral	All patients	Start from LD conditioning until 1-year post-CAR T-cell infusion AND/OR until CD4+ count >0.2 × 10^9/l Valaciclovir 500 mg bid or aciclovir 800 mg bid		
Anti-pneumocystis	All patients	To start from LD conditioning until 1-year post-CAR-T cell infusion AND/OR until CD4+ count >0.2x10 G/l Co-trimoxazole 480 mg once daily or 960 mg three times each week	In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered	Can be started later depending on center guidelines
Systemic primary anti-fungal prophylaxis	Prophylaxis may be considered in severe neutropenia (ANC <500) with a high-risk profile for ICAHT (e.g. CAR HEMATOTOX score and risk profile according to **Table 2**) and/or prolonged neutropenia	Mold-active prophylaxis for 1-3 months (depending on the duration of neutropenia and use of steroids): posaconazole (300 mg/day) or micafungin (50 mg i.v./day)		In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids (long-term >72 h, or high-dose), prophylaxis is recommended

Figure Legends

Figure 1. The CAR-HEMATOTOX score as a risk-stratification tool

Figure 2. Step-by-step diagnostic work-up depending on ICAHT severity

* In case of elevated ferritin and clinical suspicion of MAS, see **Table S3** and **Figure S1**

Figure 3. Treatment algorithm for Immune Effector Cell Associated Neutropenia

*High-risk defined as prior history of hematopoietic stem cell transplantation, baseline cytopenia, high tumor burden and systemic inflammation, presence of BM infiltration.

**Anti-fungal prophylaxis particularly recommended in patients with prior IFD, prior allo-HCT, and receiving corticosteroids (long-term >72h or high-dose). Decision for/against anti-bacterial prophylaxis should incorporate local bacterial epidemiology (e.g. prevalence for MDR GNB); not recommended for patients with a low-risk profile for ICAHT

† Also extends to late ICAHT if these criteria are met

Figure 1

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**			

Risk Profile

Low Risk (HT 0-1)

	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%

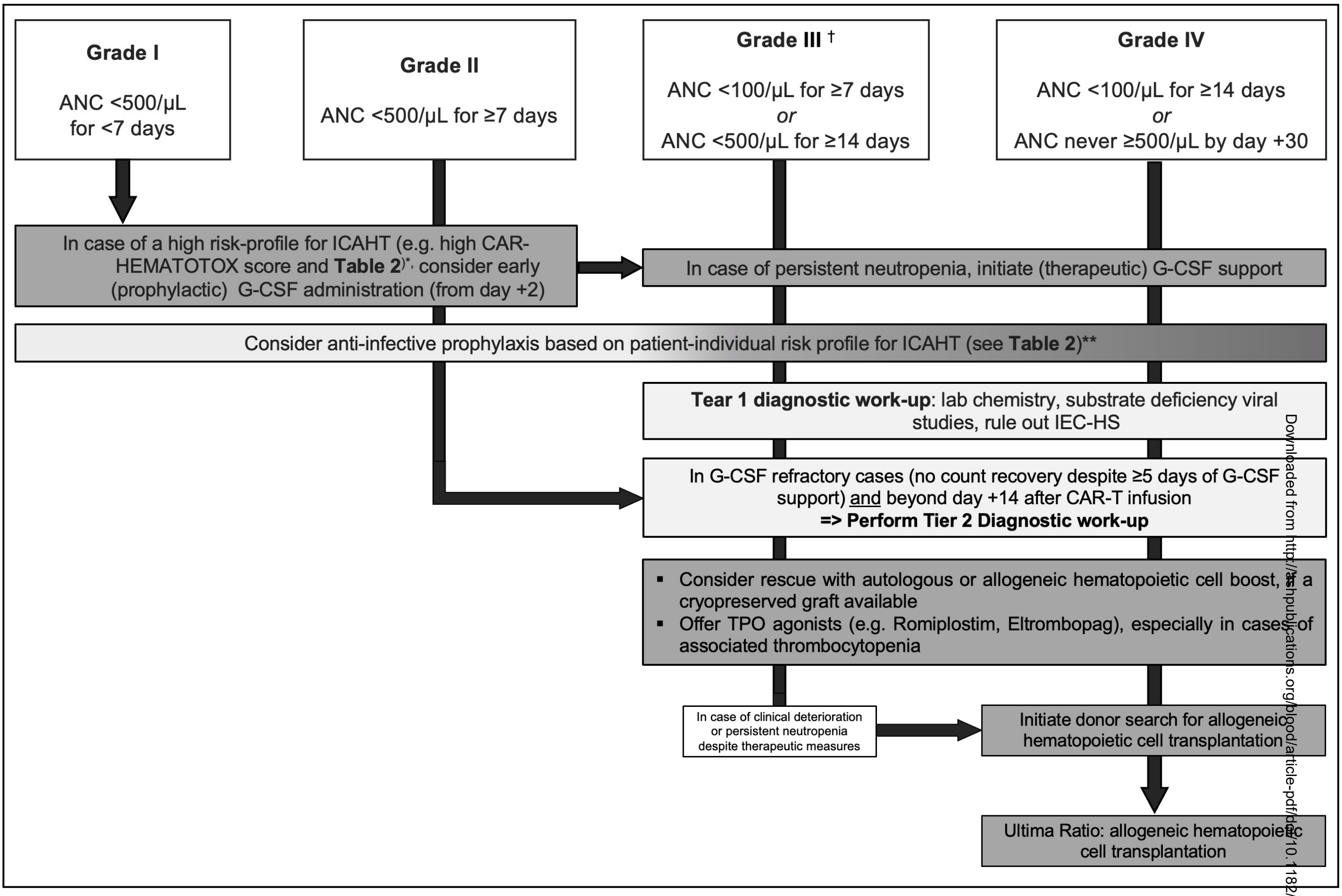
High Risk (HT 2-7)

	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 2

	Categories	Putative causes	Test	Time points	Comments from expert panel
TIER 1	Lower threshold to perform – minimal workup				
	Poor bone marrow reserve	Prior treatments including allo-HCT, fludarabine, marrow infiltration	Complete blood count (CBC), reticulocyte production index (RPI), peripheral blood smear	routinely	Recommended
	Medication – drug side effects	Check for concomitant myelosuppressive medications		routinely	
	Vitamin deficiencies	Vitamin B12, Folic acid	Serum levels	routinely	Recommended
	Rule out infections	Bacterial/ Viral/Fungal infections	Blood cultures, CMV PCR, Procalcitonin CD4^{+} T-cell, IgG, B-cell levels	routinely	Recommended
	Rule out macrophage-activation syndrome*	CRS/MAS or IEC-HS	Ferritin, triglycerides	routinely	Recommended
TIER 2	Subsequent work-up – In case of G-CSF refractory state, if tier 1 results are negative and/or risk factors are present				
	Viral PCR considering the clinical presentation	Parvovirus	Parvovirus B19 PCR	In case of prolonged anemia	Recommended
		HHV6, JC	HHV6, JC PCR blood/CSF	In case of neurologic symptoms	Recommended
		EBV, adeno, HSV	PCR	In case of HLH	Recommended
	Bone marrow disease	(MDS/AML/myelofibrosis) or relapse	BM aspirate, biopsy, Flow cytometry, immunohistochemistry, cytogenetics, NGS	In case of prolonged cytopenia	Recommended
		Relapse of leukemia/lymphoma	Flow cytometry peripheral blood / bone marrow, With B-cell panel	routinely	Recommended
	Other causes	Other rare hematologic diseases, myeloid diseases, PNH, autoimmune processes	Myeloid panel, PI-linked structures, Direct Antiglobulin Test (DAT)	In case of suspected MPN/PNH/ autoimmune processes	Recommended

Figure 3



Grade I
ANC <500/µL for <7 days
Grade II
ANC <500/µL for ≥7 days
Grade III †
ANC <100/µL for ≥7 days
or
ANC <500/µL for ≥14 days
Grade IV
ANC <100/µL for ≥14 days
or
ANC never ≥500/µL by day +30
In case of a high risk-profile for ICAHT (e.g. high CAR-HEMATOTOX score and Table 2)*, consider early (prophylactic) G-CSF administration (from day +2)
In case of persistent neutropenia, initiate (therapeutic) G-CSF support
Consider anti-infective prophylaxis based on patient-individual risk profile for ICAHT (see Table 2)**
Tear 1 diagnostic work-up: lab chemistry, substrate deficiency viral studies, rule out IEC-HS
In G-CSF refractory cases (no count recovery despite ≥5 days of G-CSF support) and beyond day +14 after CAR-T infusion
=> Perform Tier 2 Diagnostic work-up
▪ Consider rescue with autologous or allogeneic hematopoietic cell boost, if a cryopreserved graft available
▪ Offer TPO agonists (e.g. Romiplostim, Eltrombopag), especially in cases of associated thrombocytopenia
In case of clinical deterioration or persistent neutropenia despite therapeutic measures
Initiate donor search for allogeneic hematopoietic cell transplantation
Ultima Ratio: allogeneic hematopoietic cell transplantation