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

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Running head: Hematotoxicity following CAR T-cell therapy

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1 Abstract

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

22 Introduction and state-of-the-art

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

36

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

49

50 In a recent international survey led by EHA and EBMT, we identified a high degree of
51 heterogeneity both in regards to the grading and management of cytopenias.³⁶ Current grading

52 systems such as the CTCAE describe cytopenias predominantly in quantitative terms by
53 assigning severity grades according to the depth of cytopenia. However, they are difficult to apply
54 in daily practice and fail to capture the distinct nature of post-CAR-T hematopoietic reconstitution,
55 such as the biphasic and/or delayed course. Furthermore, the cumulative risk of secondary
56 complications (e.g., infections, bleeding) primarily increases with the respective duration of
57 observed cytopenia.^{22,37} Classification systems that were developed for cytopenia following
58 classic cytotoxic chemotherapies may not apply to patients receiving novel T-cell based
59 immunotherapies. To accommodate these unique features of hematological side effects in adult
60 patients receiving such therapies, we herein introduce the concept of Immune Effector Cell
61 Associated Hemato-Toxicity, or ICAHT. Based on a novel framework for grading, we outline
62 expert recommendations for its diagnostic work-up and management.

63

64 **Methodology**

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

75

76 These recommendations are intended to be general in scope and applicable to all diseases and
77 types of autologous CAR T-cell therapies or other T-cell based immunotherapies (e.g., bispecific
78 antibody constructs) adopted as standard clinical practice. They are intended to reflect current
79 best practices in this new and rapidly evolving field and aim to help clinicians and other
80 healthcare professionals in providing consistent, high-quality patient care. These
81 recommendations were created due to the growing number of autologous CAR T-cell therapies

82 currently available outside clinical trials for the treatment of hematological malignancies. Given
83 the lack of high-quality evidence from randomized trials in this area (expected Evidence Levels 3-
84 5, Oxford Centre for Evidence Based Medicine), the decision was made not to grade these
85 recommendations. They therefore represent the consensus point of view of the authors. When
86 administering CAR T-cell therapies within clinical trials, physicians are advised to follow
87 respective trial protocols.

88

89 **Consensus recommendations**

90 **1. ICAHT Grading**

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

103

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

105 The overall incidence of hematological toxicity in the key registrational trials for CAR T-cell
106 products endorsed by the European Medicines Agency (EMA) are outlined in the **Supplemental**
107 **Table 1**. Furthermore, we performed an extensive literature review of prominent real-world
108 studies with a specific focus on correlative studies and potential risk factors (**Supplemental**
109 **Table 2**). Overall, a plethora of factors contribute to the development of cytopenias after CAR-T,
110 some of which remain incompletely understood. Broadly, they relate to the underlying disease
111 and its previous treatments, baseline risk factors (e.g., hematopoietic reserve, BM infiltration,

112 systemic inflammation), as well as CAR-T product features and CRS-related inflammatory
113 patterns (summarized in **Table 2** and the **Supplementary Text**).^{12,13,23,30,33,34,39-56}

114

115 **3. What scoring systems to use**

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

134

135 **4. Assessment and diagnostic work-up of ICAHT**

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

142

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

157

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

159 Hemophagocytic lymphohistiocytosis (HLH) represents a hyper-inflammatory condition
160 resulting from abnormal immune activation, which is associated with high fever,
161 hyperferritinemia, prolonged cytopenia and eventually multi-organ failure. HLH remains a
162 diagnostic quandary as unique biomarkers are still lacking and/or not readily available. In the
163 context of CAR T-cell therapy, the incidence of HLH-like symptoms ranges from 1% to
164 3.4%.^{10,58} Two entities, CRS/MAS and IEC-HS, can be distinguished according to time of
165 onset and presence of concomitant CRS/ICANS symptoms.^{29,59-61} In patients with severe
166 ICAHT that present with aplastic neutrophil recovery and rising serum ferritin, the diagnosis of
167 HLH should be considered, as both can present with profound immune dysregulation and
168 increased IFN signaling.^{42,54} A comprehensive work-up is recommended in order to identify
169 additional abnormalities such as new-onset hepatosplenomegaly, hypertriglyceridemia,
170 coagulopathy and hypofibrinogenemia, as well as hemophagocytosis features on BM biopsy
171 or in other tissues (**Fig. 2**). Existing scoring systems that can guide the diagnosis of HLH in

172 the context of severe ICAHT include HLH-2004 criteria, the H-score, and the OHI index.⁶²⁻⁶⁴
173 Additionally, **Table S3** outlines the MD Anderson criteria⁵⁸, EBMT/EHA/JACIE
174 recommendations⁵⁹ and IEC-HS criteria⁶⁰, which were deemed more specific to CAR-T
175 therapy by the expert panel. In patients in whom ICAHT manifests in the form of HLH, anti-
176 inflammatory measures should be promptly initiated to mitigate cytokine storm and its clinical
177 sequelae. Patients should be treated with anakinra, a recombinant humanized IL-1 receptor
178 antagonist, in combination with high-dose corticosteroids (**Figure S1**). In refractory cases,
179 ruxolitinib, cytokine adsorption, and emapalumab (IFN- γ inhibitor) can be considered, albeit
180 data remains scarce.⁶⁵⁻⁶⁷

181

182 **6. Management of cytopenias**

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

188

189 **Transfusions**

190 Due to the frequent nature of severe anemia and thrombocytopenia after CAR-T therapy,
191 transfusions are an essential part of supportive care and include either packed red blood cell
192 concentrates (pRBCs) or platelet concentrates (PCs). Transfusion-associated GvHD (ta-GvHD)
193 is a rare complication of transfusion wherein viable donor T lymphocytes in cellular blood
194 products mount an immune response against the recipient.⁶⁸ Considering the high mortality rate
195 (>90%), prevention of ta-GvHD is recommended, though there is no internationally agreed upon
196 consensus on the duration of the use of irradiated blood products across cellular therapies. In
197 the setting of HCT, standard practice is to use irradiated blood for (1) at least 2 weeks prior to
198 stem cell collection until at least 3 months after auto-HCT, and (2) starting with conditioning at
199 the latest until at least 6 months after allo-HCT, or until immune reconstitution.⁶⁹ In the context
200 of CAR-T therapy, the expert panel recommended the irradiation of blood products from 7 days
201 prior to leukapheresis until at least 90 days post-CAR-T infusion unless conditioning, disease or

202 previous treatment determine indefinite duration (**Table 3**). Of note, the use of the purine
203 analogue fludarabine as a component of lymphodepletion prior to CAR-T infusion may impact
204 local guidance for irradiated blood products.⁶⁹ Given its relative rarity, we recommend reporting
205 cases of ta-GVHD following CAR-T to regulatory authorities.

206

207 **Growth factor support**

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

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

212

213 *Granulocyte colony-stimulating factor (G-CSF)*

214 Due to the concerns for the use of GM-CSF and the hypothesized, but largely unknown risks of
215 exacerbating toxicities, early guidance suggested generally deferring G-CSF until resolution of
216 acute CAR T-cell related immunotoxicity (typically week 3). However, several recent reports
217 question this as a general rule and point towards an acceptable safety profile for the early use of
218 G-CSF, with no increase of high-grade ($\geq 3^\circ$) CRS/ICANS.⁷²⁻⁷⁶ In the largest retrospective analysis
219 by Miller and colleagues (n=197), prophylactic G-CSF *before* CAR-T (mostly pegylated G-CSF)
220 was associated with faster neutrophil recovery, comparable treatment outcomes, and similar
221 rates of severe ICANS.⁷⁵ While prophylactic G-CSF was associated with a higher rate of grade ≥ 2
222 CRS, this observation did not extend to the clinically relevant grade ≥ 3 CRS. In a subgroup
223 analysis, the authors found that G-CSF did not worsen severity of CRS in patients who *already*
224 present with low-grade (1°) toxicity. In a further study by Lievin et al, early G-CSF administration
225 (from day +2) in neutropenic patients was associated with a reduced risk of febrile neutropenia
226 without increasing the risk of severe CRS or ICANS.⁷⁴ Notably, G-CSF was also safe in
227 maintaining CAR T-cell expansion kinetics and anti-lymphoma activity, without any deleterious
228 impact on the quality of response and outcomes.^{73,74} Appraising the above evidence and
229 weighing the benefits and risks, early G-CSF administration on day +2 can be considered in high-
230 risk patients to shorten the length of expected severe neutropenia (see **Table 2** and **Figure 1**).
231 Therapeutic G-CSF in case of prolonged severe neutropenia (ANC $<500/\mu\text{L}$) can also be

232 considered, and can be of diagnostic benefit for identifying the aplastic neutrophil recovery
233 phenotype^{13,32}, which is often G-CSF unresponsive. The large majority of CAR-T patients (>80%)
234 ultimately respond to growth factor support with count recovery.^{32,34} However, recurrent neutrophil
235 dips (biphasic course) can necessitate intermittent application of therapeutic G-CSF (**Figure 3**).
236 Finally, a uniform consensus was reached on the necessity of *prospective*, and ideally
237 multicenter, clinical trials that evaluate the safety and optimal treatment protocol for G-CSF
238 (prophylactic vs. early / pegylated vs. non-pegylated) in the context of CAR-T therapy and across
239 disease entities (B-ALL vs. B-NHL vs. MM).

240

241 *Thrombopoietin (TPO) agonists*

242 TPO agonists (e.g., eltrombopag, romiplostim) are considered primarily in patients with
243 prolonged and late thrombocytopenia, with the thrombocytopenic nadir typically occurring in the
244 2nd month after CAR-T therapy.^{12,13} Data supporting the use of TPO agonists in the CAR-T
245 setting are extremely limited and are restricted to a few case series from single centers with
246 limited patient numbers.⁷⁷⁻⁷⁹ In these limited reports, improvement in platelets and also
247 hemoglobin and ANC was noted, with some patients becoming transfusion independent both
248 for platelets and pRBCs similar to improvement in hematopoiesis observed with TPO agonist
249 use in cases of acquired BM failure.^{80,81} Due to the limited available data, the expert panel
250 advises that the use of TPO agonists should parallel the practice for HCT.⁸² They can also be
251 utilized in G-CSF refractory cases of ICAHT (**Figure 3**).

252

253 **Infection prophylaxis**

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

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

- 262 ▪ **Antibacterial prophylaxis:** the panel proposes a risk-adapted strategy based on the
263 patient-individual risk profile for infections including the expected incidence rate of
264 protracted, profound neutropenia (ANC <100/ μ L for \geq 7 days), in line with the consensus
265 American Society of Clinical Oncology (ASCO)/ Infectious Diseases Society of America
266 (IDSA) recommendations for adult cancer patients.⁸⁶ Antibacterial prophylaxis with a
267 fluoroquinolone (e.g. levofloxacin, ciprofloxacin) is not recommended in patients who are at
268 a low risk of severe (grade \geq III) ICAHT (**Table 1, Table 3**) and should be avoided due to
269 fluoroquinolone-specific side effects, the potential emergence of resistant strains, and
270 selection for *C. difficile* and *enterococci*.^{37,87-90} Furthermore, recent publications have
271 demonstrated that antibiotic exposure prior to CAR T-cell therapy reduces microbiome
272 diversity and is associated with inferior outcomes, potentially due to the multifunctional and
273 immunomodulatory role of the gut microbiome.⁹¹⁻⁹⁴ On the other hand, antibacterial
274 prophylaxis can be considered in high-risk patients once the ANC falls below <500/ μ L to
275 mitigate the risk of severe infections. The CAR-HEMATOTOX score may be useful for
276 guidance and identification of high-risk candidates.¹³ In a large retrospective analysis of
277 LBCL patients receiving CD19 CAR-T, a significant reduction of severe bacterial infections
278 with fluoroquinolone prophylaxis was observed in CAR-HEMATOTOX^{high} but not CAR-
279 HEMATOTOX^{low} patients, supporting a risk-adapted approach. Importantly, the panel
280 recommends adherence to institutional guidelines that take into account local epidemiology
281 and resistance patterns. In this context, monitoring for multi-drug resistant gram-negative
282 bacteria (MDR GNB) colonization (i.e., active surveillance through rectal swab culture) may
283 be useful both for baseline risk assessment and during prolonged neutropenia.
- 284 ▪ **Antifungal prophylaxis:** To reduce the risk of invasive fungal disease (IFD), anti-mold
285 prophylaxis (e.g., micafungin or posaconazole) can be considered in patients at high risk
286 for severe ICAHT (grade \geq III) once the ANC falls below <500/ μ L (**Table 3**). Additional risk
287 factors to consider are prior allo-HCT, prior invasive aspergillosis and receipt of
288 corticosteroids (either long-term \geq 72h or high-dose, e.g., greater than 10 mg of
289 dexamethasone or equivalent). The low overall incidence rate for IFD in the context of
290 CAR-T should be taken into account⁹⁵, although fungal infections represent a frequent
291 cause of fatal infectious complications.^{22,96} Systemic primary antifungal prophylaxis should

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

294

295 *Hematopoietic cell boost*

296 Patients who are unresponsive and/or refractory to G-CSF beyond day +14 after CAR-T infusion
297 represent a clinically challenging subgroup of patients at high risk for severe and even fatal
298 infectious complications. While the evidence remains limited, TPO agonists can be offered in this
299 setting, especially in cases of associated thrombocytopenia.⁷⁹ In cases of severe ICAHT in which
300 an inflammatory stressor is deemed contributory (severe CRS/ICANS, CRS/MAS), anti-
301 inflammatory strategies such as pulse-dose corticosteroids and/or anti-cytokine therapies (e.g.,
302 tocilizumab, anakinra) should be used. A promising strategy pertains to the use of cryopreserved
303 autologous or allogeneic CD34⁺ hematopoietic cells from prior collection (either prior auto- or allo-
304 HCT).⁹⁷⁻⁹⁹ Three recent case series shed light on both the safety and clinical feasibility of this
305 approach across a broad population of pediatric and adult patients (summarized in
306 **Supplemental Table 4**). High rates of sustained neutrophil and platelet engraftment were noted
307 across studies. While hematopoietic cell boost (HCB) has been successfully applied during active
308 infection¹⁰⁰, clinicians should be aware of the possibility of immune reconstitution inflammatory
309 syndrome (IRIS) in patients with prolonged bone marrow aplasia.³¹ As the earlier application of an
310 *available* HCB was associated with superior survival outcomes,⁹⁹ the expert panel recommends
311 considering the application of a HCB without prior conditioning chemotherapy for grade \geq III
312 ICAHT beyond day +14 if (1) a boost is readily available and (2) G-CSF refractoriness has been
313 established. At the same time, the survey results highlighted that even when HCB were
314 considered a viable treatment option in a patient with prior auto-HCT, they were often not
315 available. While prophylactic collection in high-risk candidates has been proposed as a potential
316 mitigating strategy, the panel cautioned that the collection process may add to the already high
317 logistic burden of CAR T-cell therapy (e.g., coordination of apheresis slots and storage capacity),
318 which could negatively impact vein-to-vein times in a state of high disease burden. Furthermore,
319 the process could incur unnecessary collection- and storage-associated costs.^{101,102} Ultimately, it
320 was concluded that further research is needed to assess the number needed to treat for
321 prophylactic stem cell collection.

322

323 *Allogeneic hematopoietic cell transplantation*

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

345

346 **7. Conclusions and Outlook**

347 Much progress has been made in the last years in defining hematological toxicity as a distinct
348 toxicity entity of CAR T-cell therapy. While the underlying pathophysiology remains incompletely
349 understood, growing evidence points towards critical interactions between host hematopoiesis
350 and CAR T-cell function and efficacy. By defining ICAHT and delineating a specific grading

351 system, we herein provide a nomenclature that enables cross-trial comparisons and invites
352 severity-based management strategies.

353

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

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- 764

765 **Main Tables and Table Legends**766 **Table 1: ICAHT Grading**

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

767 *measured ≥2 time points, or non-transient neutropenia

768

769 **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 |
| | Clonal hematopoiesis of indeterminate potential (CHIP)? | Has been linked to increased inflammation, potential emerging risk factor | Saini et al. ⁴⁶ 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 |

770 **Table 3: Short-term management of cytopenias**

| | When | How | Precautions | Comments |
|--|---|--|---|--|
| Packed red blood 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 ⁹ 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), dapsonsone 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 |

771

772 **Figure Legends**773 **Figure 1. The CAR-HEMATOTOX score as a risk-stratification tool**

774

775 **Figure 2. Step-by-step diagnostic work-up depending on ICAHT severity**776 * In case of elevated ferritin and clinical suspicion of MAS, see **Table S3** and **Figure S1**

777

778 **Figure 3. Treatment algorithm for Immune Effector Cell Associated Neutropenia**779 *High-risk defined as prior history of hematopoietic stem cell transplantation, baseline cytopenia,
780 high tumor burden and systemic inflammation, presence of BM infiltration.781 **Anti-fungal prophylaxis particularly recommended in patients with prior IFD, prior allo-HCT, and
782 receiving corticosteroids (long-term >72h or high-dose). Decision for/against anti-bacterial
783 prophylaxis should incorporate local bacterial epidemiology (e.g. prevalence for MDR GNB); not
784 recommended for patients with a low-risk profile for ICAHT

785 † 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

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 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

