

Supplementary Material

Supplementary Text

Regarding the underlying disease, direct comparison of the incidence of post-CAR-T cytopenias across trials must be performed with caution due to differences in trial design, CAR constructs, cohort sizes and patient populations. However, a varying degree and duration of hematotoxicity has been observed across disease subtypes (B-ALL, B-NHL, multiple myeloma) and depending on the target antigen (CD19, BCMA), as outlined in **Supplemental Table 1-2**. In a recent meta-analysis, a higher incidence of post-CAR-T cytopenia was observed in patients with BCP-ALL, which may be related to disease infiltration of the bone marrow at baseline and the intensive prior therapy.¹ Brudno and colleagues observed that patients with prolonged cytopenias (>2 months post-infusion) following BCMA-targeting CAR-T products were more likely to exhibit increased concentrations of CAR T-cells in the bone marrow post-infusion.² BM resident CAR T-cells may thus facilitate low-level inflammation in response to BCMA-expressing precursors, or exert off-target effects on hematopoietic stem cells (HSCs).

The majority of early cytopenias (particularly until day +10) can be explained by the applied lymphodepleting chemotherapy. Fludarabine and cyclophosphamide are the agents most frequently employed to modulate the recipient immune system in order to facilitate CAR T-cell activity and expansion. While the dose of fludarabine is well-standardized across the different protocols, different dose intensities of cyclophosphamide are utilized according to the underlying diagnosis, which may in part account for disease-specific differences in cytopenia rates. Despite the established myelotoxicity of these combinations, they are not *per se* myeloablative and hematological recovery is expected in 1-2 weeks. Importantly, the number of previous lines of therapies, and especially prior hematopoietic cell transplantation (HCT), can substantially impact BM reserve and baseline hematopoietic function.^{1,3} In line with this observation, bridging therapy has been reported to affect cytopenias before CAR-T infusion.⁴ Since the disease burden before CAR-T administration is associated with the overall treatment outcome after infusion,⁵ the intensity of the bridging therapy should be tailored according to the disease status, carefully evaluating the risks and the benefits, to avoid prolonged toxicity or severe infections which may impair the final outcome. Notably, baseline cytopenias (especially thrombocytopenia) represent a potent risk factor for

the development of ICAHT.^{6,7} The presence of BM infiltration (especially with a high degree of malignant cells) can further increase this risk, and represents an independent risk factor of severe hematotoxicity across disease entities (e.g. LBCL, MCL, multiple myeloma).⁸⁻¹⁰ Marrow infiltration may predispose for local inflammatory processes within the BM niche, but can also reflect progressive disease and high tumor burden (e.g. high baseline lactate dehydrogenase levels), which have also been linked to post-CAR-T hematopoietic recovery.

Among the pre-infusion factors, there is a growing interest regarding the role of clonal hematopoiesis of indeterminate potential (CHiP), which is more common in patients exposed to cytotoxic therapies and has been shown to predispose for hyper-inflammatory responses, including in the context of CAR-T therapy.¹¹⁻¹³ Such clones may predispose for the development of therapy-related myeloid neoplasms, which represent an important differential diagnosis of late-onset cytopenias after CAR T-cell therapies.¹⁴ CHiP clones may also contribute to the degree of systemic inflammation at baseline, which has been demonstrated to associate with prolonged neutropenia in the form of elevated serum levels of CRP and ferritin at time of lymphodepletion. These markers have not only been linked to a pro-inflammatory tumor microenvironment prior to CAR-T therapy, but also suppressive myeloid cells and inflammatory cytokines in the peripheral blood.¹⁵ Such underlying immune dysregulation may propagate HSC dysfunction.⁸

Regarding CAR-T product features, patients treated with CD28z-endodomain CAR-T cells displayed higher rates of delayed blood count recovery, which may relate to the increased rate of severe CAR-T immunotoxicity and concomitant hyperinflammation that accompanies the rapid *in vivo* CAR-T expansion observed with CD28z CAR-T products.^{1,7,16-19} The impact of CAR construct design on hematotoxicity remains to be elucidated. However, in a recent meta-analysis, Xia et al reported an association between increased cytopenia rates after CAR-T and the use of lentiviral vectors for viral transduction (as opposed to γ -retroviral vectors), as well as for dual-targeting therapies (e.g. bicistronic constructs, tandem CARs).¹ While the potential mechanism was not clearly stated, both enhanced immune toxicity and immune responses may be contributory. Notably, severe CRS or ICANS (grade 3-4) often precede the onset of prolonged low blood cell counts, and CRS-related cytokine patterns have been associated with prolonged cytopenias (e.g. elevated interleukin [IL]-6, IL-18, monocyte chemoattractant protein-1 [MCP-1], interferon

[IFN]- γ).^{3,7,20,21} Moreover, an enrichment of interferon signaling within the HSC compartment of BM aspirates has been noted.²² This observation is also in line with previous studies which have reported that IFN- γ can impair self-renewal and skew the differentiation of HSCs.^{23,24} Finally, other factors might contribute to the pathophysiology of ICAHT and events such as viral infections, sepsis, and relapse of the underlying disease should be considered in the differential diagnosis.

References

1. Xia Y, Zhang J, Li J, et al. Cytopenias following anti-CD19 chimeric antigen receptor (CAR) T cell therapy: a systematic analysis for contributing factors. *Ann Med*. 2022;54(1):2951-2965.
2. Brudno JN, Natrakul D, Lam N, Dulau-Florea A, Yuan CM, Kochenderfer JN. Acute and delayed cytopenias following CAR T-cell therapy: an investigation of risk factors and mechanisms. *Leuk Lymphoma*. 2022;63(8):1849-1860.
3. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant*. 2019;54(10):1643-1650.
4. Roddie C, Neill L, Osborne W, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. *Blood Adv*. 2023.
5. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR-T cell therapies for large B-cell lymphoma in Germany. *Blood*. 2022.
6. Rejeski K, Perez Perez A, Sesques P, et al. CAR-HEMATOTOX: A model for CAR T-cell related hematological toxicity in relapsed/refractory large B-cell lymphoma. *Blood*. 2021.
7. Juluri KR, Wu V, Voutsinas JM, et al. Severe cytokine release syndrome is associated with hematologic toxicity following CD19 CAR T-cell therapy. *Blood Adv*. 2021.
8. Rejeski K, Perez Perez A, Iacoboni G, et al. Biphasic Neutrophil Recovery after CD19 CART in R/R LBCL Is Associated with Superior PFS/OS, Robust CAR T-Cell Expansion in Relation to Baseline Tumor Volume, and a Decrease of Systemic Inflammation over Time. *Blood*. 2022;140(Supplement 1):4549-4551.
9. Rejeski K, Wang Y, Albanyan O, et al. The CAR-Hematotox Score Identifies Patients at High Risk for Hematological Toxicity, Infections and Poor Clinical Outcomes Following Brexucabtagene Autoleucel in Relapsed/Refractory Mantle Cell Lymphoma. *Blood*. 2022;140(Supplement 1):651-653.
10. Rejeski K, Hansen DK, Bansal R, et al. The CAR-Hematotox Score As a Prognostic Model of Toxicity and Response in Patients Receiving BCMA-Directed CAR-T for Relapsed/Refractory Multiple Myeloma. *Blood*. 2022;140(Supplement 1):7506-7508.

11. Liu Y, Derkach A, Lewis N, et al. Clonal hematopoiesis in diffuse large B-cell lymphoma: clinical impact and genetic relatedness to lymphoma and therapy-related myeloid neoplasm. *Haematologica*. 2023;108(3):917-922.
12. Saini NY, Swoboda DM, Greenbaum U, et al. Clonal Hematopoiesis Is Associated with Increased Risk of Severe Neurotoxicity in Axicabtagene Ciloleucel Therapy of Large B-Cell Lymphoma. *Blood Cancer Discov*. 2022;3(5):385-393.
13. Miller PG, Sperling AS, Brea EJ, et al. Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. *Blood Adv*. 2021;5(15):2982-2986.
14. Cordeiro A, Bezerra ED, Hirayama AV, et al. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. *Biol Blood Marrow Transplant*. 2020;26(1):26-33.
15. Jain MD, Zhao H, Wang X, et al. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. *Blood*. 2021;137(19):2621-2633.
16. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10):2145-2154.
17. Luo W, Li C, Zhang Y, et al. Adverse effects in hematologic malignancies treated with chimeric antigen receptor (CAR) T cell therapy: a systematic review and Meta-analysis. *BMC Cancer*. 2022;22(1):98.
18. Kawalekar OU, RS OC, Fraietta JA, et al. Distinct Signaling of Coreceptors Regulates Specific Metabolism Pathways and Impacts Memory Development in CAR T Cells. *Immunity*. 2016;44(3):712.
19. Zhao Z, Condomines M, van der Stegen SJC, et al. Structural Design of Engineered Costimulation Determines Tumor Rejection Kinetics and Persistence of CAR T Cells. *Cancer Cell*. 2015;28(4):415-428.
20. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. *Blood Adv*. 2020;4(15):3776-3787.
21. Wang Y, Song Z, Geng Y, et al. The risk factors and early predictive model of hematotoxicity after CD19 chimeric antigen receptor T cell therapy. *Front Oncol*. 2022;12:987965.
22. Li X, Deng Q, Henderson J, et al. Targetable Cellular Etiology of Prolonged Cytopenia Following CD19 CAR T-Cell Therapy. *Blood*. 2022;140(Supplement 1):4502-4503.
23. de Bruin AM, Demirel O, Hooibrink B, Brandts CH, Nolte MA. Interferon-gamma impairs proliferation of hematopoietic stem cells in mice. *Blood*. 2013;121(18):3578-3585.
24. Morales-Mantilla DE, King KY. The Role of Interferon-Gamma in Hematopoietic Stem Cell Development, Homeostasis, and Disease. *Curr Stem Cell Rep*. 2018;4(3):264-271.

Supplementary Tables

Trial / Product	Disease / Target / Endodomain / Vector	Lymphodepletion	CRS all (≥G3), %	Month 1 Neutropenia, %	Prolonged Neutropenia, %	Month 1 Thrombocytopenia, %	Prolonged Thrombocytopenia, %	Ref.
ELIANA Tisa-cel	Pediatric ALL / CD19 / 4-1BBz / LV	Flu 30 mg/m ² x 4d Cy 500 mg/m ² x 2d	77 (46)	≥ G3: 53*	≥ G3: 20*	≥ G3: 41*	≥ G3: 29*	Maude et al. NEJM 2018
ZUMA-3 Brexu-cel	Adult ALL / CD19 / CD28z / RV	Flu 25mg/m ² x 3 Cy 900mg/m ² x1	93 (31)	≥ G3: 22*	n.r.	36 (≥ G3: 33)*	n.r.	Shah et al. Blood 2021
ZUMA-1 Axi-cel	Adult LBCL / CD19 / CD28z / RV	Flu 30mg/m ² x 3d Cy 500 mg/m ² x 3d	86 (14)	36 (≥ G3:26)	19 (≥ G3: 11)	41 (≥ G3:24)	18 (≥ G3:7)	Locke et al. Mol Ther 2017 / Lancet 2019
JULIET Tisa-cel	Adult LBCL / CD19 / 4-1BBz / LV	Flu 25 mg/m ² x 3d Cy 250 mg/m ² x 3d	58 (22)	≥ G3:24	≥ G3: 0	≥ G3:41	≥ G3: 38	Schuster et al. NEJM 2019
TRANSCEND Liso-cel	Adult LBCL / CD19 / 4-1BBz / LV	Flu 30 mg/m ² x 3d / Cy 300 mg/m ² x 3d	42 (2)	63 (≥ G3:60)	≥ G3:7	31 (≥ G3:27)	≥ G3: 22	Abramson et al. Lancet 2020
ZUMA-2 Brexu-cel	Adult MCL / CD19 / CD28z / RV	Flu 30mg/m ² x 3d / Cy 500 mg/m ² x 3d	91 (15)	87 (≥ G3:85)	74 (≥ G3:51)	≥ G3:16	≥ G3:16	Wang et al. NEJM 2020 / JCO 2023
ZUMA-5 Axi-cel	Adult FL / CD19 / CD28z / RV	Flu 30mg/m ² x 3d / Cy 500 mg/m ² x 3d	82 (7)	≥ G3: 33	n.r.	≥ G3: 15	n.r.	Jacobson et al Lancet Oncol 2022
ZUMA-7 Axi-Cel	Adult LBCL / CD19 / CD28z / RV	Flu 30mg/m ² x 3d / Cy 500 mg/m ² x 3d	92 (6)	17 (≥ G3:13)	33 (≥ G3:26)	9 (≥ G3:4)	19 (≥ G3:6)	Locke et al. NEJM 2022
TRANSFORM Liso-Cel	Adult LBCL / CD19 / 4-1BBz / LV	Flu 30 mg/m ² x 3d / Cy 300 mg/m ² x 3d	50 (1)	n.r.	≥ G3: 37	n.r.	≥ G3: 37	Kamdar et al. Lancet 2022
KarMMa Ide-cel	Adult MM / BCMA / 4-1BBz / LV	Flu 30mg/m ² x 3d / Cy 300 mg/m ² x 3d	84 (5)	≥ G3: 40	28	≥ G3: 48	27	Munshi et al. NEJM 2021
CARTITUDE-1 Cilta-cel	Adult MM / BCMA / 4-1BBz / LV	Flu 30mg/m ² x 3d / Cy 300 mg/m ² x 3d	95 (4)	≥ G3: 30	≥ G3: 10	≥ G3: 41	≥ G3: 26	Berdeja et al. Lancet 2021 Martin et al. JCO 2023

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

Axi-cel: axicabtagene ciloleucel; B-ALL: B-cell acute lymphoblastic leukemia; BCMA: B-cell maturation antigen; brexu-cel: brexucabtagene autoleucel; CD: cluster of differentiation; cilta-cel: ciltacabtagene autoleucel; CRS: cytokine release syndrome; cy: cyclophosphamide; d: day; FL: follicular lymphoma; flu: fludarabine; ide-cel: idecabtagene vicleucel; G grade; M1: neutropenia / thrombocytopenia at 1 month; MCL: mantle cell lymphoma; MM: multiple myeloma; n.r.: not reported; LBCL: large B-cell lymphoma; LV: lentiviral vector; Liso-Cel: lisocabtagene maraleucel; RV: γ-retroviral vector; tisa-cel: tisagenlecleucel.

* reported as “decreased neutrophil counts” / “decreased platelet counts”

Reference	# patients / Disease	Product / Target / Costimulatory domain	CRS all (≥G3), %	Month 1 Neutropenia, %	Prolonged Neutropenia, %	Month 1 Thrombocytopenia, %	Prolonged Thrombocytopenia, %	comments
Nahas et al. Leuk Lymph 2020	N=21 LBCL	Axi-cel	n.r.	≥ G3: 38		n.r.	n.r.	2 cases of MDS
Fried et al. BMT 2019	N=35 ALL, NHL	Local product / CD19 / CD28	77 (14)	95 (≥ G3:50)	95 (≥ G3:65)	78 (≥ G3:23)	80 (≥ G3:23)	Biphasic neutropenia and thrombocytopenia; proposed mechanism for late CART cytopenia: SDF-1 alterations
Cordeiro et al. BBMT 2020	N=86 ALL, NHL, CLL	Local product / CD19 / 4-1BB	n.a.	Cytopenia > d 90: 16%				4 cases of MDS, long-lasting nature of cytopenia after CAR-T
Jain et al. Blood Adv 2020	N=83 BCL, ALL MM	Axi-cel, Tisa-cel, Local product/ CD19 (ALL: CD28), BCMA (MM: 4-1BB)	84 (23)	70 (≥ G3:67)	29 (≥ G3:20)	77 (≥ G3:49)	66 (≥ G3:10)	Delayed hematopoietic recovery associated with high-grade CRS/ICANS MDS (n=1)*
Sesques et al. AJH 2020	N=61 BCL	Axi-cel, Tisa-cel	85 (8)	n.r.	65 (≥ G3: 36)	n.r.	88 (≥ G3: 48)	
Strati et al. Haematologica 2021	N=31 LBCL	Axi-cel	97 (10)	≥ G3:28	n.r.	≥ G3:42	n.r.	MDS (n=4)**
Rejeski et al. Blood 2021	N=235 LBCL	Axi-cel, Tisa-cel	87 (11)	≥ G3: 91		≥ G3: 62		Description of 3 typical phenotypes of post CAR-T neutrophil recovery: quick vs. intermittent vs. aplastic; Development of CAR-HEMATOTOX score with independent validation
Wang et al. Front Oncol 2021	N=76 ALL	Local product / CD19; CD22; CD19+CD22 / 4-1BB	82 (38)	70		48		
Nagle et al. AJH 2021	N=31 DLBCL	Axi-cel, Tisa-cel	0	n.r.	≥ G3: 58	n.r.	≥ G3: 48	
Logue et al. Haematologica 2021	N=85 LBCL	Axi-Cel	93 (9)	71 (≥ G3 30)	38 (≥ G3 13)	80 (≥ G3 26)	52 (≥ G3 5)	Description of long-term immune reconstitution
Logue et al. Blood Adv 2022	N=52 MM	Ide-Cel	85 (6)	63 (≥ G3: 39)	36 (≥ G3: 11)	90 (≥ G3: 51)	66 (≥ G3: 28)	Real-world data on hematotoxicity in multiple myeloma
Juluri et al. Blood Adv 2022	N=173 ALL, NHL, CLL	Local product / CD19 / 4-1BB	70 (15)	80 (≥ G3: 46)	76 (≥ G3: 38)	81 (≥ G3: 34)	75 (≥ G3: 51)	FU (40 M): persistent neutropenia (9%) and thrombocytopenia (14%) Association of hematotoxicity with high-grade CRS and CRS-related inflammatory patterns
Bethge et al. Blood 2022	N=319 LBCL	Axi-cel, Tisa-cel	73 (12)	≥ G4: 81	≥ G4:17	37	12	Delayed hemtopoietic recovery associated with NRM
Bachy et al. Nat Med 2022	N=418 DLBCL	Axi-cel, Tisa-cel	81 (7)	43 (≥ G3: 17)	20 (≥ G3: 23)	43 (≥ G3: 16)	20 (≥ G3: 6)	Matched-paired comparison of CAR products; increased hematotoxicity incidence with Axi-cel > Tisa-cel
Gauthier et al. Blood 2022	N=129 NHL	Axi-cel, Tisa-cel, investigational product(JCAR-014; 4-1BB)	74 (5)	≥ G3: 37		≥ G3: 38		
Wang et al. Cytotherapy 2023	N=93 MM	Local product / BCMA / n.r.	93 (41)	72 (≥ G3: 39)	n.r.	77 (≥ G3: 59)	n.r.	Impact of cytokine patterns on post-CAR-T hematopoietic recovery

Supplemental Table 2: Incidence of post CAR-T cytopenias in the real-world setting.

Axi-cel: axicabtagene ciloleucel; ALL: acute lymphoblastic leukemia; BCL: B-cell lymphoma; BCMA: B-cell maturation antigen; brexu-cel: brexucabtagene autoleucel; CD: cluster of differentiation; CLL: chronic lymphocytic leukemia; CRS: cytokine release syndrome; d: day; DLBCL: diffuse large B cell lymphoma; FU: 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; n.r.: not reported; 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.

	HLH-2004 (for fHLH)	H-score (for all sHLH/MAS)	MD Anderson	CRS/MAS	IEC-HS	Comments for CRS/MAS and ICE-HS
CRS				Refractory CRS	onset with resolving/resolved CRS or worsening inflammatory response after initial improvement	
Fever	X	X		X (++)	X	Can be absent in pts under steroids and in ICE-HS
New-onset Organomegaly	X	X		X (+/-)	X	Useful to discriminate between CRS and CRS/MAS
Pulmonary manifestations			X		X	
Renal insufficiency			X		X	
CNS involvement					X	Overlapping with ICANS
Severe cytopenia	X	X		X (++)	X	Always present Progression or new onset of cytopenias can be observed in ICE-HS
serum transaminases/ or bilirubin		X	X	X (+)	X	Can be seen in CRS, change in the kinetic (ie biphasic)
Serum ferritin	X	X	X	X (++)	X (> 2 x UL of normal or baseline at CART infusion) and/or rapidly rising (pre-requisite)	Can be seen in CRS, change in the kinetic (ie biphasic)
LDH					X	Non specific
Hypo-fibrinogenemia	X	X		X (+/-)	X	Often due to liver dysfunction
Hyper-triglyceridemia	X	X		X (+)	X	Often due to liver dysfunction
Haemophagocytosis in marrow or other tissue	X	X	X	X (+++)	X	To differentiate potential overlapping syndrome, represents an important tool in the diagnostic algorithm for CRS/MAS
Coagulopathy				X (+/-)	X	Often due to liver dysfunction
Low/absent NK cell activity	X					Not routinely used
sIL-2r (CD25)	X					Not routinely used

Supplemental Table 3: HLH diagnosis criteria, including in the context of CAR-T therapy

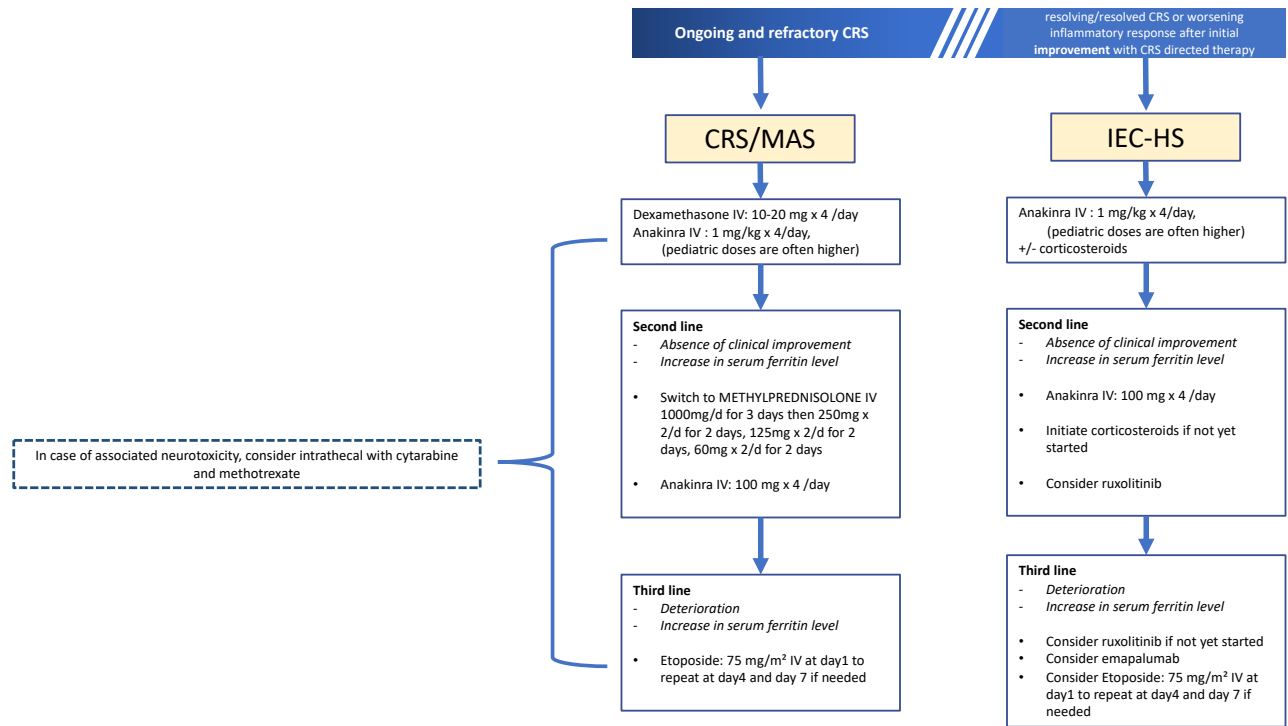
Abbreviations. HLH: haemophagocytic lymphohistiocytosis; fHLH: familial HLH; sHLH: secondary HLH; CRS: cytokine release syndrome; MAS: macrophage activation syndrome; IEC-HS: immune effector cell associated HLH-like syndrome; CNS: central nervous system; ICANS: immune effector cell associated neurotoxicity syndrome; UL: upper level; LDH: lactodehydrogenase; NK: natural killer; sIL-2r: soluble IL-2 receptor.

	Rejeski et al.	Mullanfiroze et al.	Gagelmann et al.
n	12	7	31
Entities	9 LBLCL, 2 BCP-ALL, 1 MCL	BCP-ALL, all pts post allo SCT	29 LBCL, 1 BCP-ALL, 1 MCL
Median Age at CAR-T infusion	57 (36 -71)	15	61
CAR Product	9 Axi-Cel, 2 Tisa-Cel, 1 Brexu-Cel	4 auto CD19 CART, 1 auto CD19/CD22 CART, 1 allo CD19 CART	20 Axi-Cel, 7 Tisa-Cel, 1 Brexu-Cel, 3 Allo CD19 CART
Prior Tx Lines	4 (2-8)		
Bridging Tx	11/12		24/31
Day of SC Boost after CAR-T	69 (36 - 617)	75 (57 – 495)	43 (7 - 442)
Stem Cell Source	9 Auto SCT; 3 Allo SCT	SCT donor	30 auto SCT; 1 allo SCT
CD34 selection	5/12 (3/3 in allo SCT)	7/7	1/1 allo SCT
Median no. of CD34 cells	3.1 x 10 ⁶ /kg KG, (Range 1.7 – 7.5)	6.75 x 10 ⁶ , (Range 2.5 – 11.2 x 10 ⁶)	3.6 x 10 ⁶ /kg KG, (Range 1.1. – 11.5)
Engraftment	10/12		26/31
Median Day of Neutrophil Engraftment	15 (6 - 124)*	42 (11 - 192) **	9 (7 - 14) ***
Median Day of Platelet Engraftment	21 (12 - 34)****	33	
1 year OS	55%	2/7 alive at last FU (2 Relapse, 2 Infection, 2 Therapy related)	59%
Remarks by the Authors	Feasible, Safe, Successful Engraftment in most, more successful if applied early	CRS can occur due to normal CD19 ⁺ Progenitors in the Graft	1-year OS in pts with Neutropenia < 38 days: 85% vs > 38 days: 44%

Supplemental Table 4: Case Series studying autologous and allogeneic stem cell boost

*Neutrophil Engraftment: ANC >0.5 G/L without growth factor support ≥3 days, **ANC >1,0 G/L without growth factor support. ***ANC > 0,5 G/L irrespective of growth factor support or sustained improvement > 1.5 G/L despite G-CSF administration. **** Platelet Engraftment: > 20 G/L, transfusion independence > 7 days.

Supplementary Figures



Supplemental Figure 1 Management of CRS/MAS and IEC-HS

Adapted from Hayden et al. (*Annals of Oncology*, 2022) and Hines et al. (*TCT*, 2023)

Anti-IL-6 therapy is generally not recommended due to lack of evidence for efficacy in late-onset IEC-HS without concomitant CRS, and as most patients will have already received tocilizumab for CRS prior to the onset of IEC-HS (Hines et al TCT 2023). Abbreviations. HLH: hemophagocytic lymphohistiocytosis; CRS: cytokine release syndrome; CRS/MAS: term to describe refractory CRS associated with macrophage activation; IEC-HS: immune effector cell associated HLH-like syndrome.