ACCADEMIA di FORMAZIONE

SIMTI

Aggiornamenti in medicina trasfusionale: dalla produzione alla terapia con emocomponenti

Gestione trasfusionale del paziente sottoposto a CAR-T cell therapy

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U.O. Medicina Trasfusionale

Ospedale Policlinico San Martino di Genova

Il sottoscritto **Gianluca Ubezio**, in qualità di Relatore
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

OSSERVATORIO TERAPIE AVANZATE

CAR-T (TERAPIA GENICA)

NOME	INN*	AZIENDA / ENTE	SOMMINISTRAZIONE E VETTORE	INDICAZIONE	APPROVAZIONE EUROPEA	AIC* IN EUROPA	AIC* IN ITALIA
Kymriah®	tisagenlecleucel		ex vivo lentivirus	leucemia linfoblastica acuta a cellule B e linfoma diffuso a grandi cellule B	agosto 2018 farmaco orfano	✓	✓ i Classe H* agosto 2019
				linfoma follicolare recidivante o refrattario	maggio 2022	✓	✓ luglio 2023
Yescarta®	axicabtagene ciloleucel		ex vivo retrovirus	linfoma diffuso a grandi cellule B e linfoma primitivo del mediastino a grandi cellule B refrattari o recidivanti	agosto 2018 farmaco orfano	✓	✓ i Classe H* novembre 2019
				linfoma follicolare recidivante o refrattario	giugno 2022	✓	✓ novembre 2023
				linfoma diffuso a grandi cellule B e linfoma a cellule B di alto grado con ricaduta entro 12 mesi o refrattari	ottobre 2022	✓	✓ i novembre 2023
Tecartus™	brexucabtagene autoleucel		ex vivo retrovirus	linfoma a cellule mantellari recidivante o refrattario	dicembre 2020 farmaco orfano	✓	✓ i Classe H* marzo 2022
				leucemia linfoblastica acuta da precursori delle cellule B recidivante o refrattaria	settembre 2022	✓	✓ i novembre 2023

tabella aggiornata a gennaio 2026

OSSERVATORIO TERAPIE AVANZATE

CAR-T (TERAPIA GENICA)

NOME	INN*	AZIENDA / ENTE	SOMMINISTRAZIONE E VETTORE	INDICAZIONE	APPROVAZIONE EUROPEA	AIC* IN EUROPA	AIC* IN ITALIA
Abecma®	idecabtagene vicleucel		**ex vivo** lentivirus	mieloma multiplo **recidivante o refrattario**	**agosto 2021** farmaco orfano	✓	✓i Classe H* **gennaio 2024**
Breyanzi®	lisocabtagene maraleucel		**ex vivo** lentivirus	DLBCL, linfoma primitivo del mediastino a grandi cellule B (PMBCL) e linfoma follicolare (FL3B)	aprile 2022	✓	✓i Classe H* **gennaio 2024**
				linfoma a grandi cellule B refrattario o recidivante (HGBCL)	luglio 2023	✓	✓i Classe H* **ottobre 2025**
				linfoma follicolare recidivato o refrattario	marzo 2025	✓	✓i Classe H* **ottobre 2025**
				linfoma mantellare recidivato o refrattario	novembre 2025	✓	✗
Carvykti™	ciltacabtagene autoleucel		**ex vivo** lentivirus	mieloma multiplo **recidivante o refrattario**	**maggio 2022** farmaco orfano	✓	✓ Classe C* **marzo 2025**

tabella aggiornata a gennaio 2026

OSSERVATORIO TERAPIE AVANZATE

CAR-T (TERAPIA GENICA)

NOME	INN*	AZIENDA / ENTE	SOMMINISTRAZIONE E VETTORE	INDICAZIONE	APPROVAZIONE EUROPEA	AIC* IN EUROPA	AIC* IN ITALIA
Aucatzyl®	obecabtagene autoleucel		ex vivo lentivirus	leucemia linfoblastica acuta da precursori di cellule B recidivante o refrattaria	luglio 2025 farmaco orfano	✓	✗

AI Overview

As of mid-2024, approximately 35,000 to over 40,000 patients worldwide have been treated with commercial CAR T-cell therapies since the first approval in 2017, with roughly 10,000 patients treated in 2024 alone. The EBMT registry surpassed 10,000 patients in Europe by September 2024, highlighting rapid adoption, though access remains limited. International Society for Cell & Gene T... +4

OSSERVATORIO TERAPIE AVANZATE

CAR-T (TERAPIA GENICA)

NOME	INN*	AZIENDA / ENTE	SOMMINISTRAZIONE E VETTORE	INDICAZIONE	APPROVAZIONE EUROPEA	AIC* IN EUROPA	AIC* IN ITALIA
Aucatzyl®	obecabtagene autoleucel		ex vivo lentivirus	leucemia linfoblastica acuta da precursori di cellule B recidivante o refrattaria	luglio 2025 farmaco orfano	✓	✗

- **Total Treated:** Estimates suggest between 34,000 and 35,480 patients received commercial CAR-T, according to reports in early to mid-2024.
- **Regional Data:** In Europe, registries have recorded over 10,000 patients. Specific analyses showed 17–42% of eligible relapsed/refractory LBCL patients received CAR-T in various EU countries between 2020–2022.
- **Access Limitations:** Despite increasing numbers, only about 25% of patients with multiple myeloma referred for CAR-T in some US centers received the treatment, with manufacturing capacity and wait times cited as major constraints.
- **Future Projections:** While ~10,000 were treated in 2024, the eligible population is expected to rise to nearly 2 million by 2029. International Society for Cell & Gene T... +4

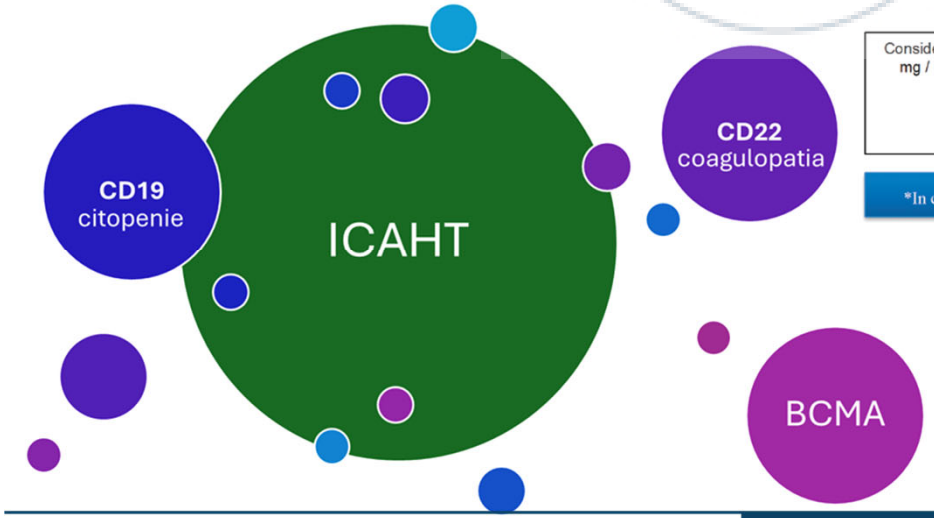
SINDROME DA RILASCIO CITOCHINICO (CRS)

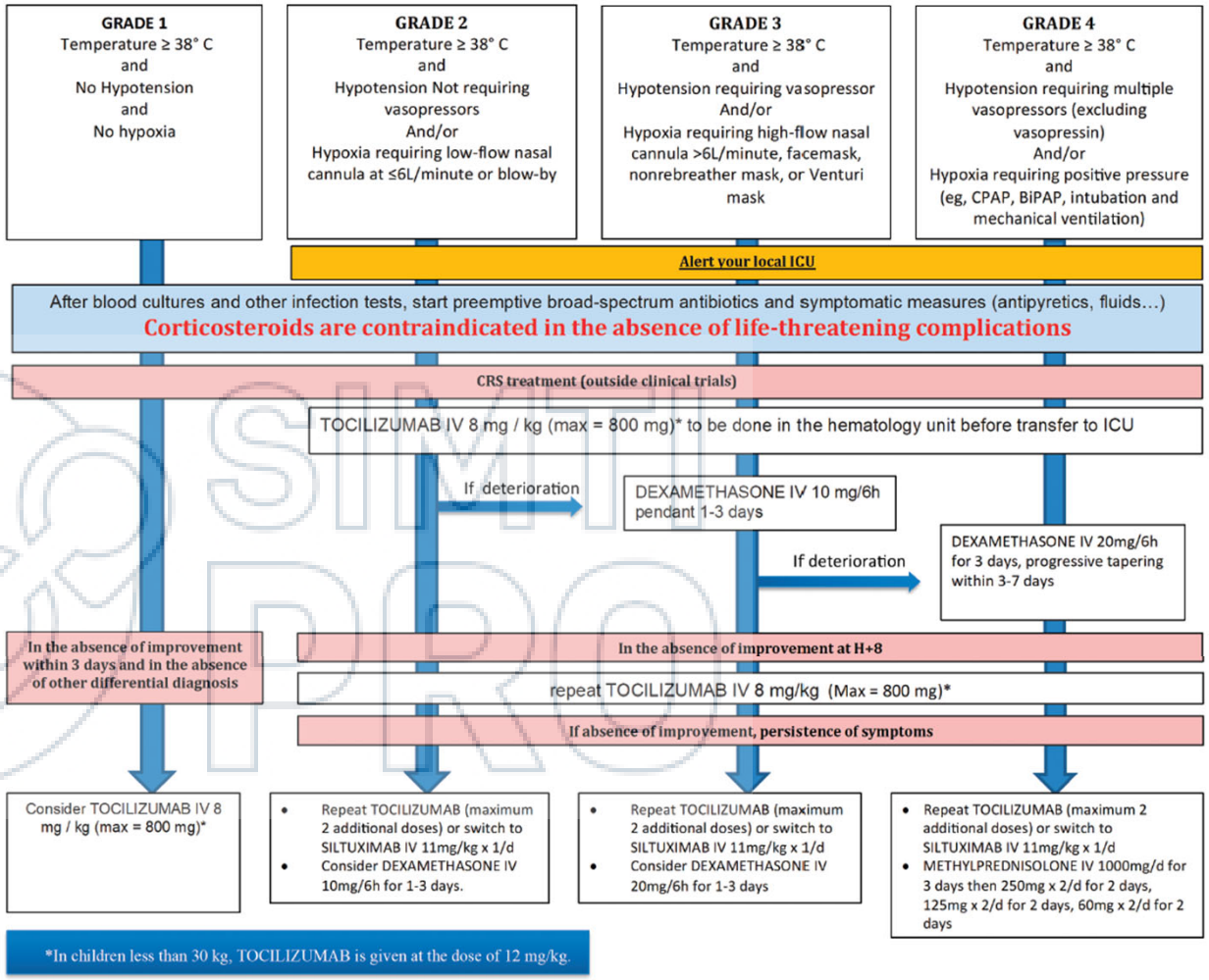
Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)

Haematologica 2018
Volume 105(2):297-316

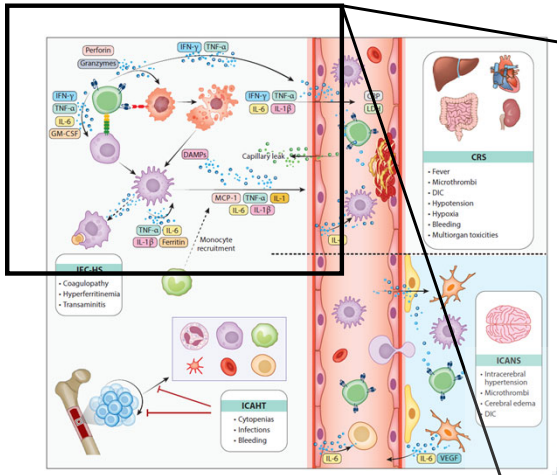
Fattori di rischio per lo sviluppo di CRS:

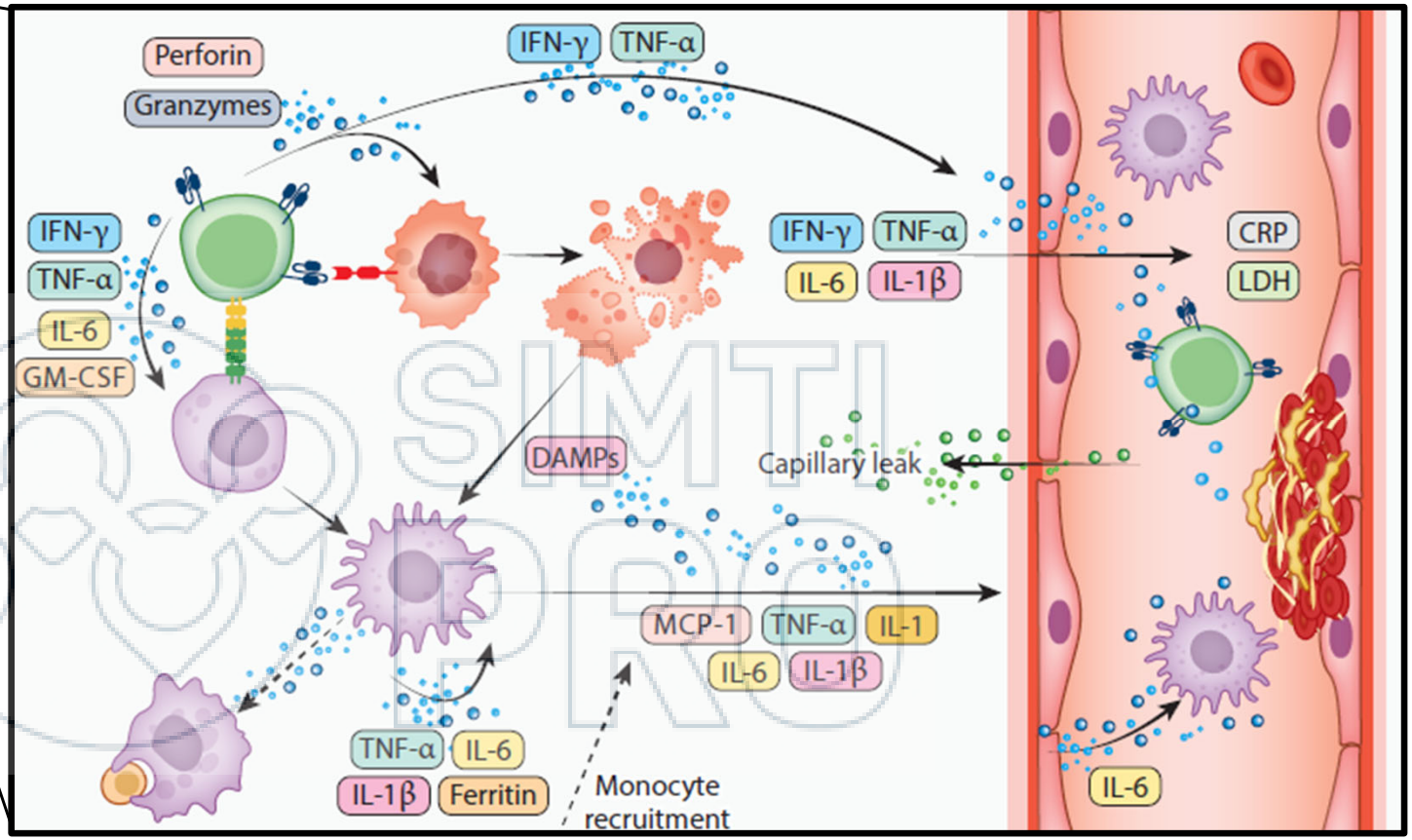
- Linfodeplezione chemioterapica pre-infusione (fludara),
- Entità della massa tumorale,
- Forte espansioen della popolazione CAR T, post-infusione,
- Target (anti-CD19 ve anti-BCMA; CD28 vs 4-1BB)





FISIOPATOLOGIA





Azione delle CAR T cells

Induzione di piroptosi delle cellule target

Rilascio DAMPs

Richiamo monocito-macrofagi

Rilascio IL-1, IL-1β e IL-6

CRS

\+

\-

Anakinra (IL-1)

Tocilizumab (IL-6)

Siltuximab (IL-6)

Annu. Rev. Med. 2026. 77:219–37

I fattori che condizionano il rischio di citopenia dopo il trattamento con CAR T cells comprendono l'infiammazione e la disregolazione del sistema immunitario, oltre alla riduzione della riserva midollare.
Quest'ultima è fortemente condizionata dal numero e dalla tipologia dei trattamenti precedent, inclusi irradiazione e storia precedente di auto- ed allotrapianto.

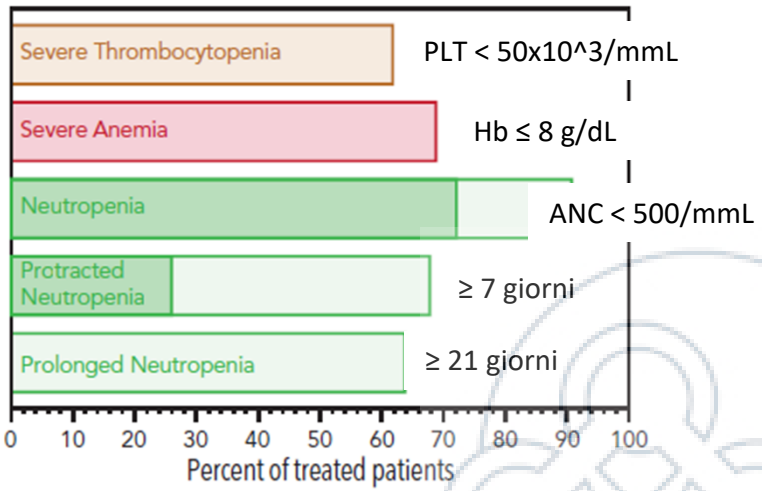
IMMUNE EFFECTOR CELL–ASSOCIATED HEMATOTOXICITY (ICAHT)

Definizione:
Una o più citopenie, a seguito di infusione di CAR T cell therapy. Si distingue tra forme **PRECOCI** (meno di 30 giorni dal trattamento) o **TARDIVE** (più di 30 giorni).

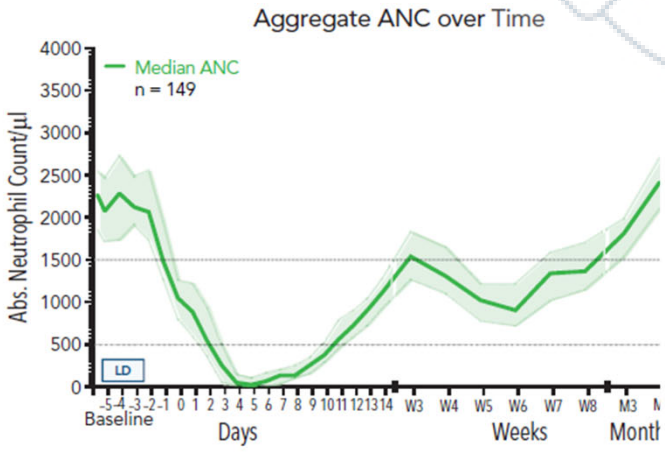
La **forma precoce** è poco distinguibile dalla normale citopenia indotta da chemioterapia, somministrata prima della infusione delle CAR T cells. Tipicamente si presenta come peggioramento, dopo una iniziale ripresa dell'emopoiesi, post-CHT (andamento bifasico).

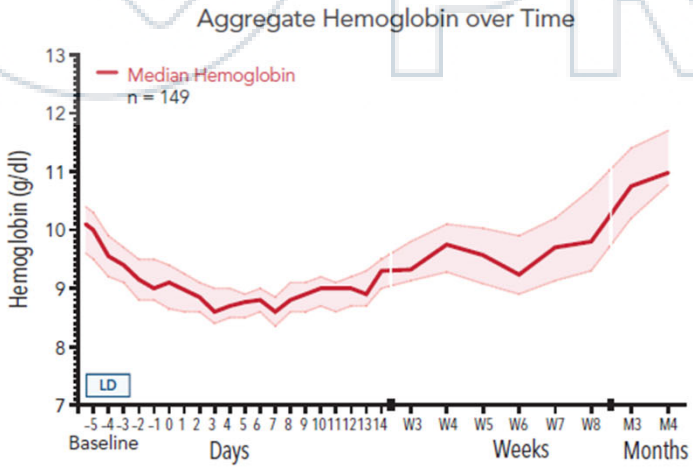
La **forma tardiva**, invece è più facilmente caratterizzabile e si osserva in 1/3 dei pazienti trattati con anti-CD19 CAR T cell therapy. La sua durata può contrarsi per settimane o mesi e comporta un peggioramento della qualità di vita (astenia) o un aumento di mortalità (infezioni, rischio emorragico).

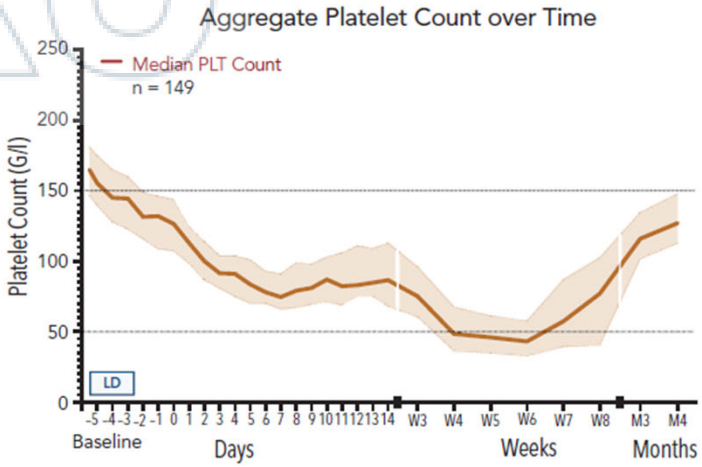
CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma



Characteristic	All patients (n = 258)	Training cohort (n = 58)	European validation cohort (n = 91)	United States validation cohort (n = 109)
Median age, y (range)	63 (19-83)	59.5 (19-74)	62 (27-83)	64 (19-79)
Median no. of previous lines of therapy (range)	3 (2-11)	4 (2-9)	3 (2-9)	3 (2-11)
Previous ASCT	69 (27)	22 (38)	27 (30)	20 (18)
CAR product				
4-1BB (tisa-cel)	88 (34)	17 (29)	51 (56)	20 (18)
CD28z (axi-cel)	170 (66)	41 (71)	40 (44)	89 (82)
Disease entity				
DLBCL	176 (68)	38 (65)	57 (63)	81 (74)
PMBCL	15 (6)	5 (9)	6 (6)	4 (4)
Transformed lymphoma*	67 (26)	15 (26)	28 (31)	24 (22)







Blood (2021); 138(24): 2499-513

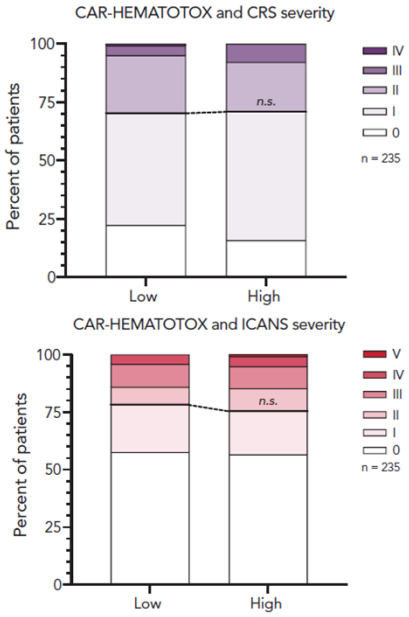
CAR-HEMATOTOX SCORE

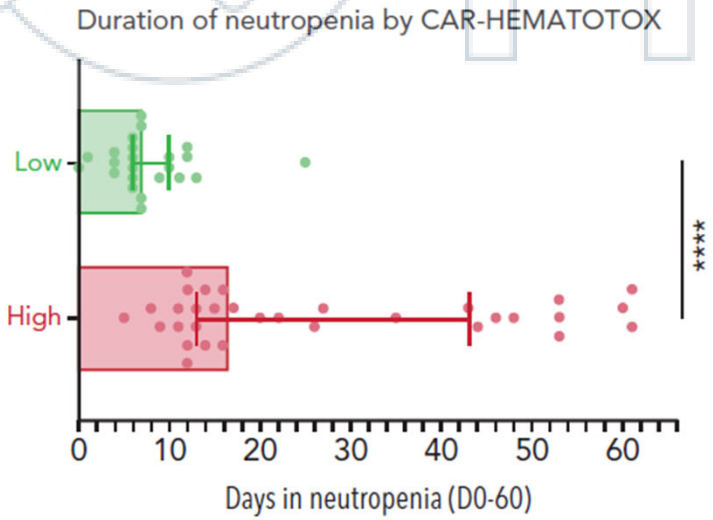
Baseline Features	0 Point	1 Point	2 Points
Platelet Count	> 175,000/µl	75,000 – 175,000/µl	< 75,000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650 – 2000 ng/ml	> 2000 ng/ml
Low: 0-1	High: ≥ 2		

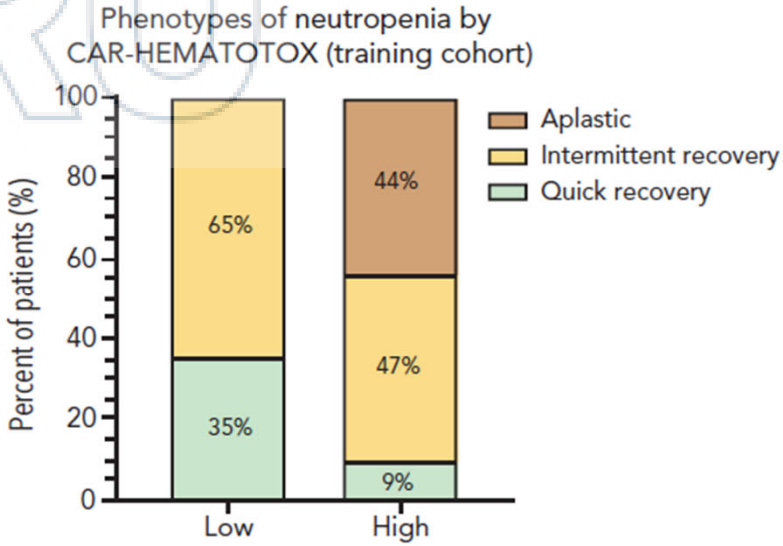
Sistema di predizione del rischio di emato-tossicità, pre-linfodeplezione.

5 parametri: i tre parametri ematologici (WBC, Hb e PLT), Prot C r., ferritina.

Non predittivo di CRS e ICANS







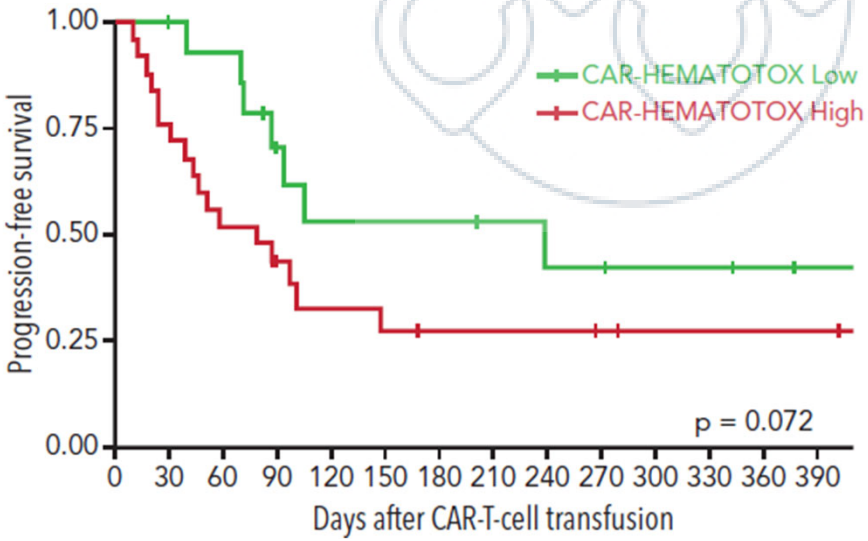
Blood (2021); 138(24): 2499-513

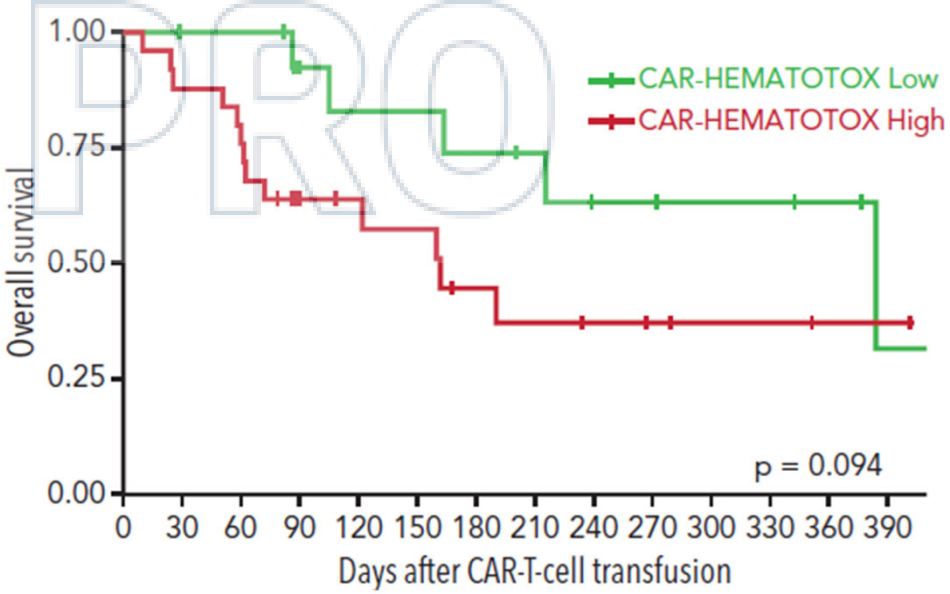
CAR-HEMATOTOX SCORE

Baseline 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		

Sistema di predizione del rischio di emato-tossicità, pre-linfodeplezione.

5 parametri: i tre parametri ematologici (WBC, Hb e PLT), Prot C r., ferritina.





Blood (2021); 138(24): 2499-513

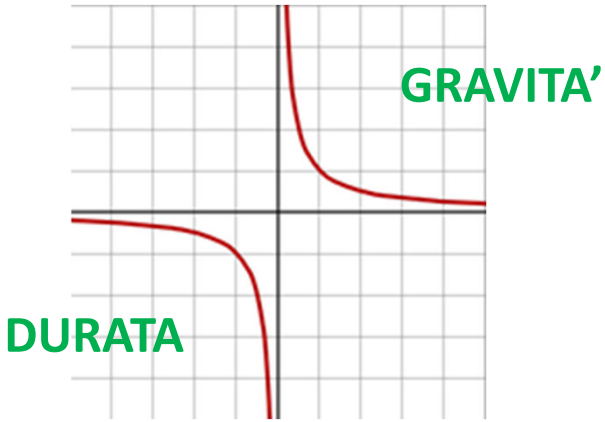
ANEMIA

IEC-associated Anemia by Depth (Top) and Duration (Bottom)

Immune Effector Cell-associated Anemia by Depth and Duration

Grade 1: Mild, N (%)	Grade 2: Moderate, N (%)	Grade 3: Severe, N (%)	Grade 4: Life-threatening, N (%)	Grade 5: Fatal, N (%)
Hemoglobin < LLN, 26 (52)	**Hemoglobin <10 g/dL, 28 (56)**	**Hemoglobin <8 g/dL, 24 (48)**	Transfusion dependency (>1 transfusion weekly), 13 (26)	**Death directly attributable to anemia-related event, 48 (96)**
Hemoglobin <10 g/dL, 22 (44)	Hemoglobin <8 g/dL, 17 (34)	Requiring no more than a single transfusion weekly, 11 (22)	Severe transfusion dependency (approximately daily), 14 (28)	Other, 2 (4)
Hemoglobin <8 g/dL, 0 (0)	Requiring no more than a single transfusion weekly, 3 (6)	Transfusion dependency (>1 transfusion weekly), 11 (22)	**Severe complication related to anemia requiring urgent intervention, 22 (44)**	
Other, 2 (4)	Other, 2 (4)	Other, 4 (8)	Other, 1 (2)	

Grade 1: Very Short, N (%)	Grade 2: Short, N (%)	Grade 3: Long, N (%)	Grade 4: Very Long, N (%)
≤7 d, 37 (74)	**≤14 d, 32 (64)**	>14 d, 9 (18)	>21 d, 3 (6)
≤14 d, 9 (18)	≤21 d, 6 (12)	>21 d, 10 (20)	>28 d, 14 (28)
≤21 d, 2 (4)	≤28 d, 9 (18)	**>28 d, 24 (48)**	**>60 d, 17 (34)**
Other, 2 (4)	Other, 3 (6)	>60 d, 5 (10)	>90 d, 14 (28)
		Other, 2 (4)	Other, 2 (4)



HemaSphere (2023)7:5

PIASTRINOPENIA

IEC-associated Thrombocytopenia by Depth (Top) and Duration (Bottom)

Immune Effector Cell-associated Thrombocytopenia by Depth and Duration

Grade 1: Mild, N (%)	Grade 2: Moderate, N (%)	Grade 3: Severe, N (%)	Grade 4: Life-Threatening, N (%)	Grade 5: Fatal, N (%)
Platelet count <150 10^9/L, 13 (26)	Platelet count <100 10^9/L, 10 (20)	Platelet count <50 10^9/L, 15 (30)	Transfusion dependency (>1 transfusion weekly), 19 (38)	**Death directly attributable to thrombocytopenia-related event, 49 (98)**
Platelet count <100 109/L, 28 (56)	**Platelet count <50 10^9/L, 27 (54)**	Platelet count <30 10^9/L, 6 (12)	**Bleeding event requiring urgent intervention, 21 (42)**	Other, 1 (2)
Platelet count <50 10^9/L, 2 (4)	Platelet count <30 10^9/L, 0 (0)	**Platelet count <20 10^9/L, 17 (34)**	Other, 10 (20)	
Platelet count <30 10^9/L, 1 (2)	Platelet count <20 10^9/L, 3(6)	Platelet count <10 10^9/L, 3 (6)		
Platelet count <20 10^9/L, 0 (0)	Requiring no more than a single transfusion weekly, 0 (0)	Transfusion dependency (>1 weekly), 1 (2)		
Other, 6 (12)	Other, 10 (20)	Bleeding event (not immediately life-threatening), = (0)		
		Other, 8 (16)		

Grade 1: Very Short, N (%)	Grade 2: Short, N (%)	Grade 3: Long, N (%)	Grade 4: Very Long, N (%)
≤4 d, 25 (50)	**≤7 d, 20 (40)**	>7 d, 9 (18)	>10 d, 0 (0)
≤7 d, 16 (32)	≤10 d, 9 (18)	>10 d, 15 (10)	>14 d, 6 (12)
≤10 d, 7 (14)	≤14 d, 17 (34)	**>14 d, 15 (30)**	>21 d, 6 (12)
Other, 2 (4)	Other, 4 (8)	>21 d, 6 (12)	**>28 d, 19 (38)**
		>28 d, 12 (24)	>60 d, 15 (30)
		Other 3 (6)	Requiring stem cell boost, 2 (4)
			Other, 2 (4)

HemaSphere (2023)7:5

Immune effector cell–associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations

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)

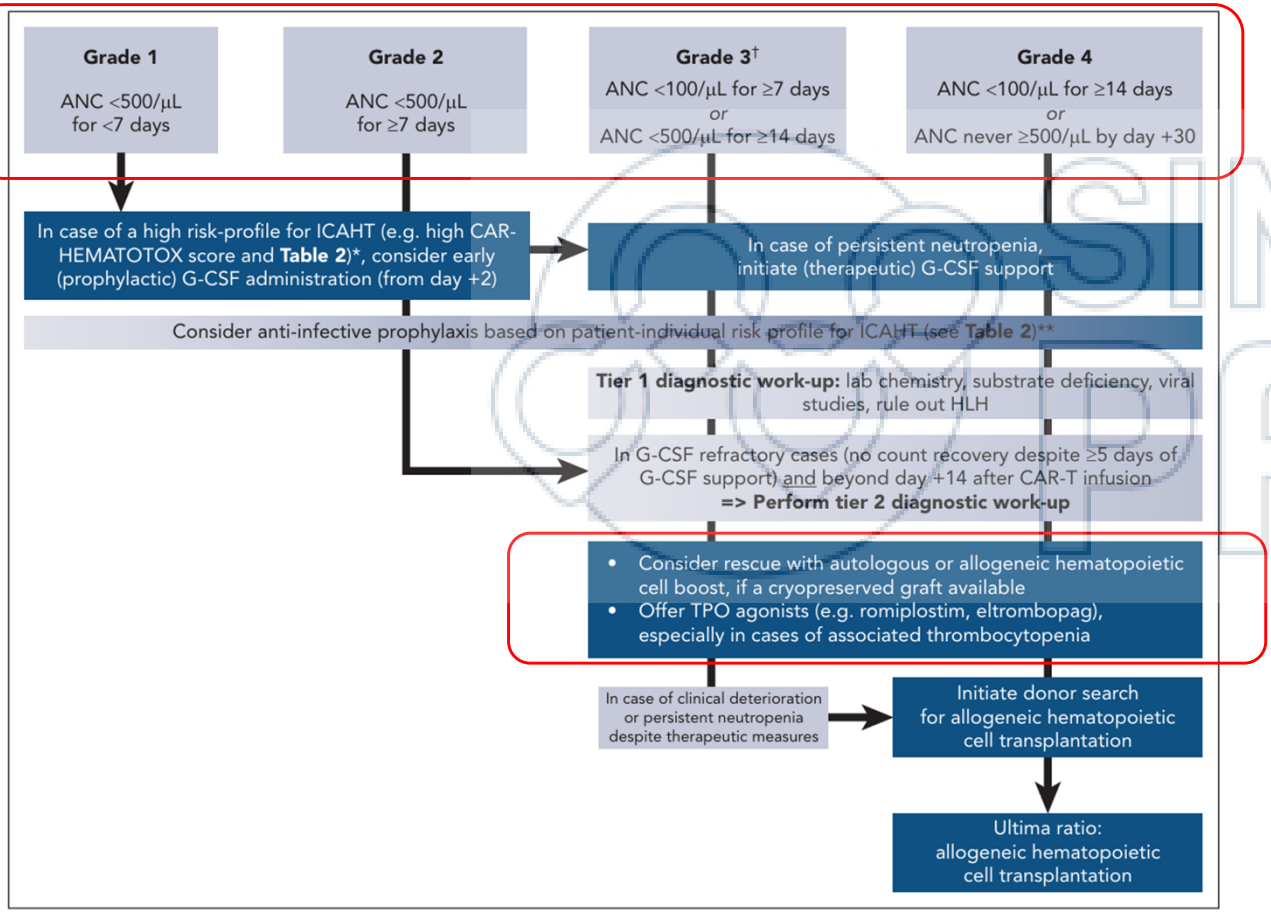
Risk profile

	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%

Blood (2023); 142(10): 865-77

	When	How	Precautions	Comments
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[68]	Irradiation of blood products; start 7 d before leukapheresis until at least 90 d after CAR T-cell infusion	Because of the use of fludarabine



Blood (2023); 142(10): 865-77

7 giorni prima

non meno di 90 giorni dopo

Cochrane Database of Systematic reviews | Review - Intervention

Restrictive versus liberal red blood cell transfusion strategies for people with haematological malignancies treated with intensive chemotherapy or radiotherapy, or both, with or without haematopoietic stem cell support

Version published: 23 May 2024

Is there a benefit of using a lower red blood cell level (restrictive) compared to a higher red blood cell level (liberal) to determine the need for red blood cell transfusion in patients diagnosed with blood cancers (e.g. leukaemia, lymphoma, myeloma) requiring intensive treatments for their disease (chemotherapy or stem cell transplantation)?

https://doi.org/10.1002/14651858.CD011305.pub3

What did we find?

• Nine studies met our inclusion criteria; seven were completed and two were still ongoing. The completed studies were conducted between 1997 and 2022 and included 540 participants. One RCT included children receiving a stem cell transplant, and it was stopped early due to safety concerns (six children). The other five RCTs only included adults, 239 adults with acute leukaemia receiving chemotherapy, and 315 with blood cancer receiving a stem cell transplant. The Hb threshold of both the restrictive (70 to 80 g/L) and liberal (80 to 120 g/L) strategies varied across the studies. The sources of funding were reported in all seven studies. One study was sponsored by industry.

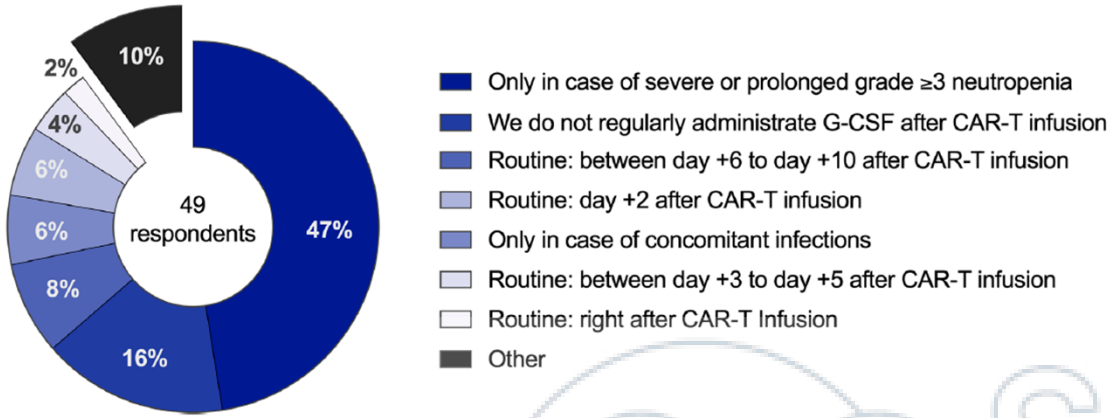
What are the limitations of the evidence?

• The included studies were at considerable risk of bias; the estimates of how the different strategies impacted the outcomes, particularly mortality, had a wide range of possible benefit or harm with too few people to be certain, and a large amount of the evidence was specifically for people with acute leukaemia and blood cancers treated with stem cell transplantation. Most studies experienced a significant number of deviations from the protocols which could have the potential to impact many outcomes due to the rationale for deviations not being well documented. Studies included in the review almost exclusively involved adult participants with only one study included which enroled six paediatric participants.

*If we assume a mortality rate of 3% within 100 days, we would need a total of **1492 participants** to have an 80% chance of detecting, at a 5% level of significance, an increase in all-cause mortality from 3% to 6%. Further RCTs are needed overall, particularly in children*

https://doi.org/10.1002/14651858.CD011305.pub3

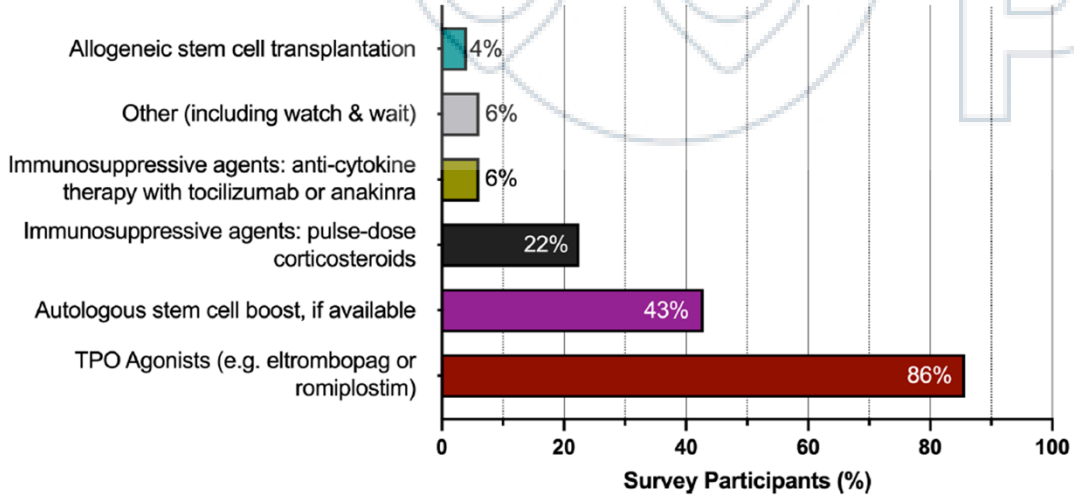
When do you on average initiate growth factor support for the management of severe or prolonged hematotoxicity?



Practice patterns concerning G-CSF use for prolonged cytopenias. G-CSF = granulocyte colony-stimulating factor.

*« For **neutropenia**, the most frequently encountered strategy was an **autologous hematopoietic cell boost**, when available (63%), followed by **TPO agonists** (43%) and immunosuppression using pulse-dose glucocorticoids (20%)»*

How have you managed immune effector cell associated thrombocytopenia refractory to G-CSF support (after ruling out all other causes other than CAR T-cell treatment)?



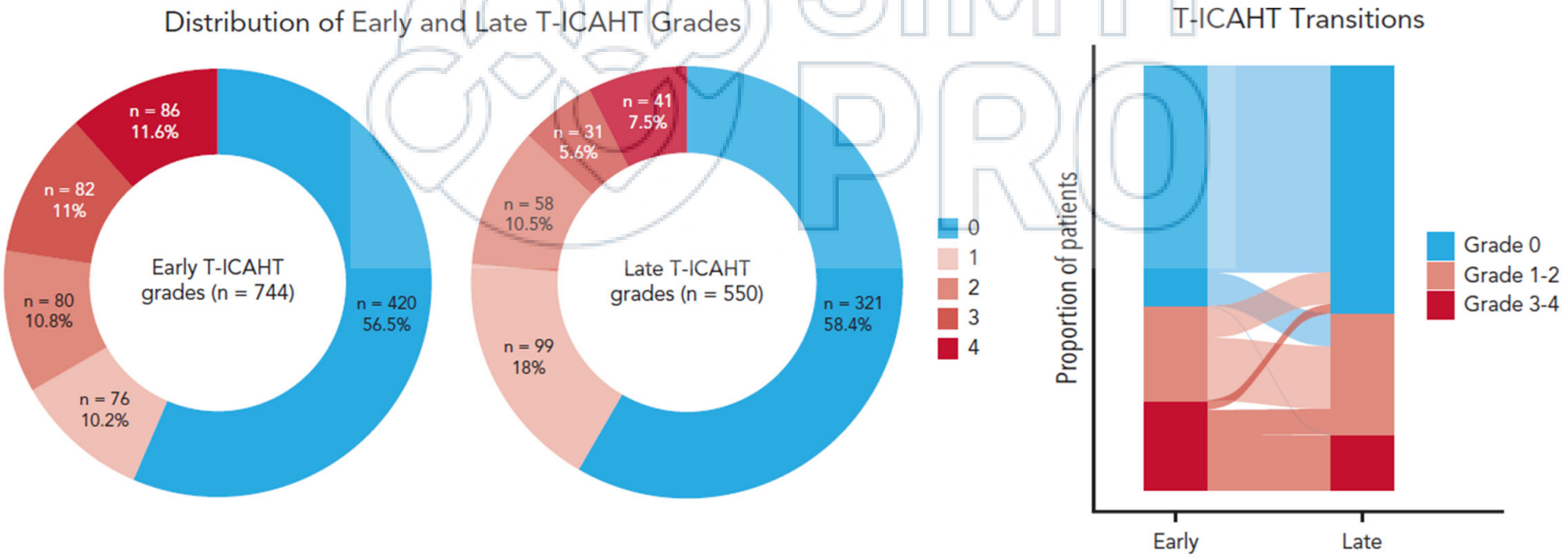
*«In contrast, the top 2 choices were inverted for the management of **thrombocytopenia**: **TPO agonists** were the most popular choice (86%) followed by **autologous hematopoietic cell boost**, if available (43%). Pulse-dose glucocorticoids were applied in 22% of survey participants, while all other options were used in <10% of cases»*

HemaSphere (2023)7:5

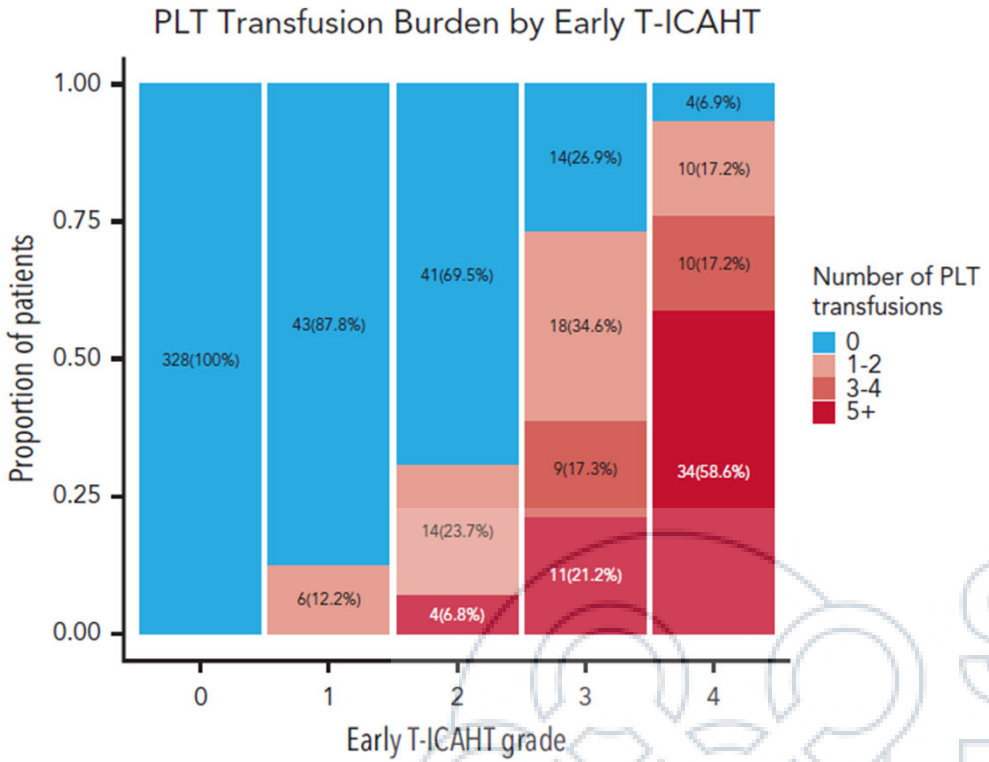
T-ICAHT: grading and prognostic impact of thrombocytopenia after CAR T-cell therapy

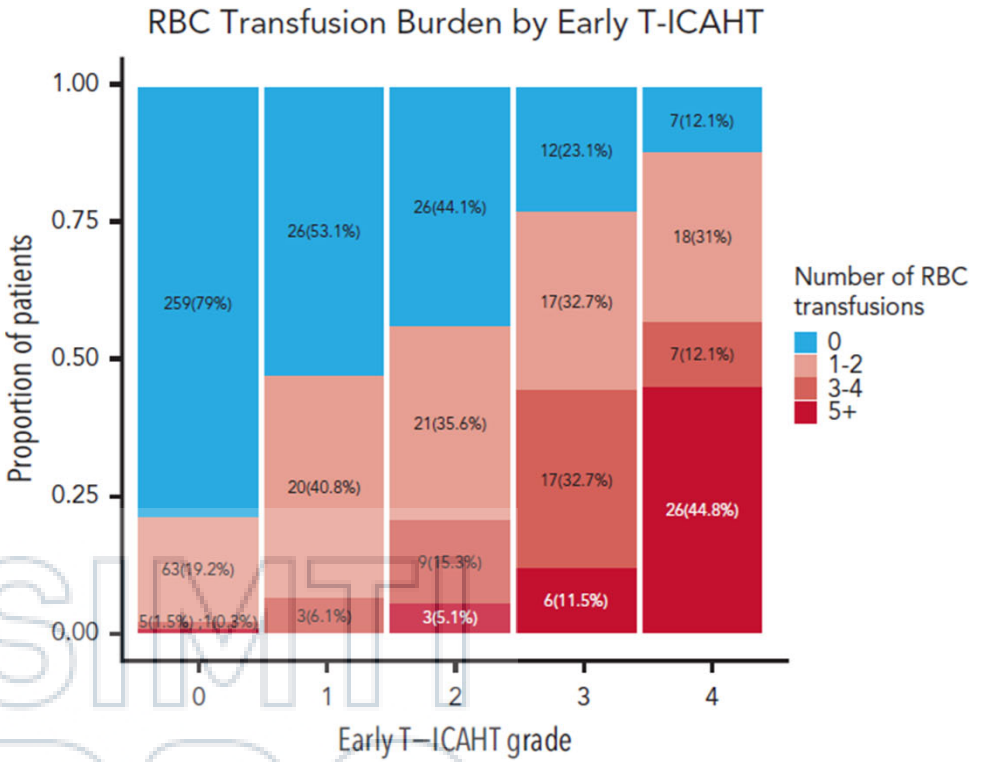
Definition of T-ICAHT grading

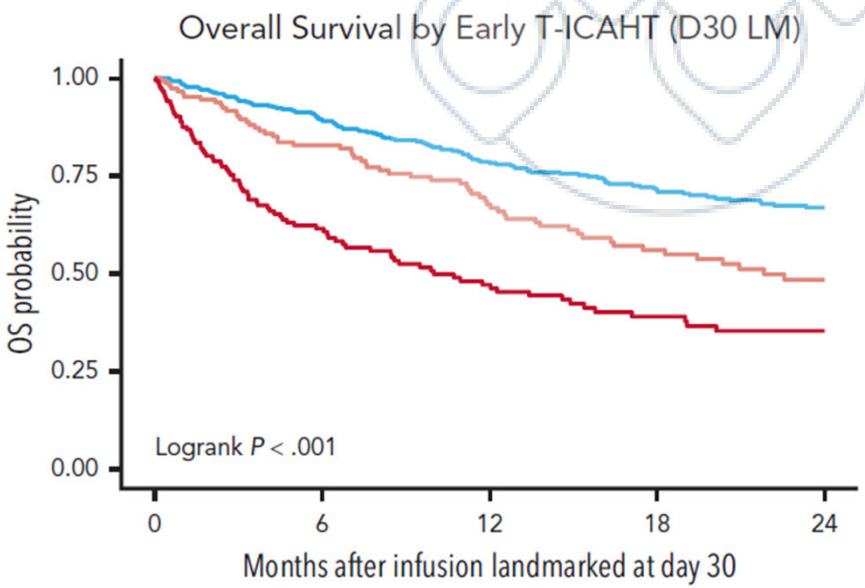
	Grade 1	Grade 2	Grade 3	Grade 4
Early T-ICAHT (days 0-30), d	—	—	—	—
PLT count <50 × 10^9/L	1-6	≥7	—	—
PLT count <20 × 10^9/L	—	—	1-13	≥14
Late T-ICAHT (days 31-100),* d	—	—	—	—
PLT count <100 × 10^9/L	≥1	—	—	—
PLT count <50 × 10^9/L		≥1		
PLT count <20 × 10^9/L	—	—	1-13	≥14

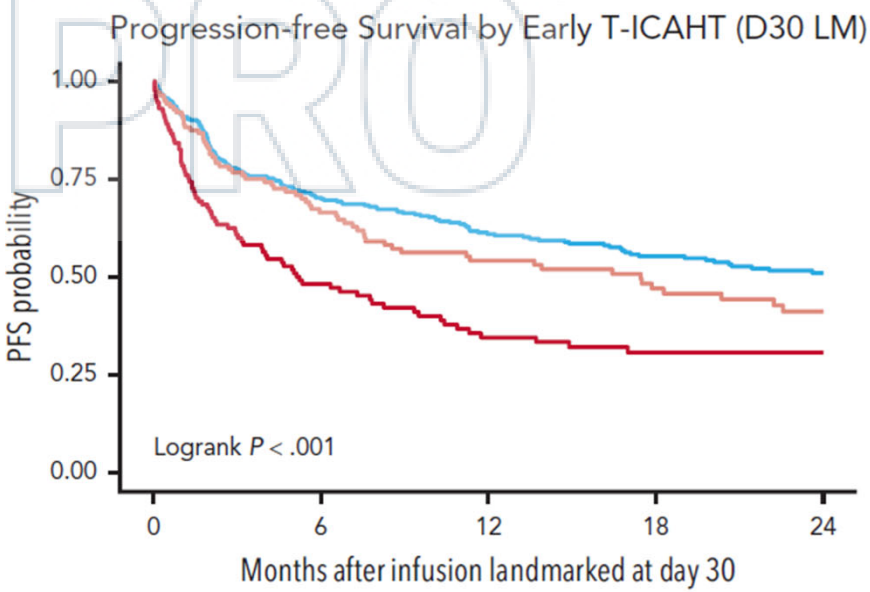


Blood (2025); 146(7): 834-46









Blood (2025); 146(7): 834-46

STRATEGIE DI MIGLIORAMENTO

Stratificazione del rischio dei singoli pazienti, con interventi profilattici o precoci

Caratterizzazione molecolare del prodotto CAR T, nella sua **interazione** con il sistema immunitario del paziente

Inibizione citochinica

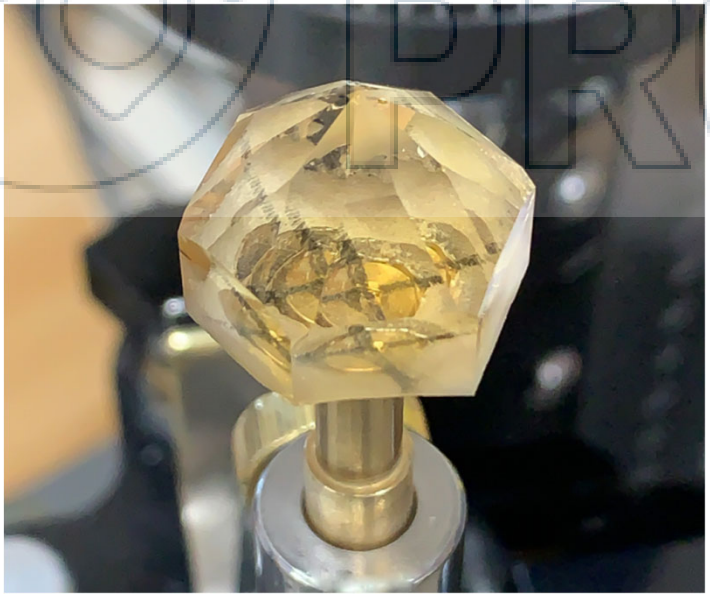
Miglioramento dei **costrutti CAR**

Miglioramento dello **stato di salute emopoietico** del paziente avviato a trattametno ovvero miglioramento della finestra di trattamento

CONCLUSIONI

Strategia classificativa evidence-based degli stati di tossicità ematologica

Forte evidenza di correlazione tra le necessità di supporto trasfusionale ed outcome clinico



Limitatezza di RCT sulla terapia trasfusionale nel setting della patologia oncoematologica.