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GRUPO 2

Complicações da terapia CAR-T: Uma abordagem prática

Palestrantes:

André Antunes (Hospital Dr. Nélio Mendonça - Funchal)

Cátia Almeida (ULS de Coimbra)

Francys Llanos (IPO de Lisboa)

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Complicações da terapia CAR-T: Uma abordagem prática

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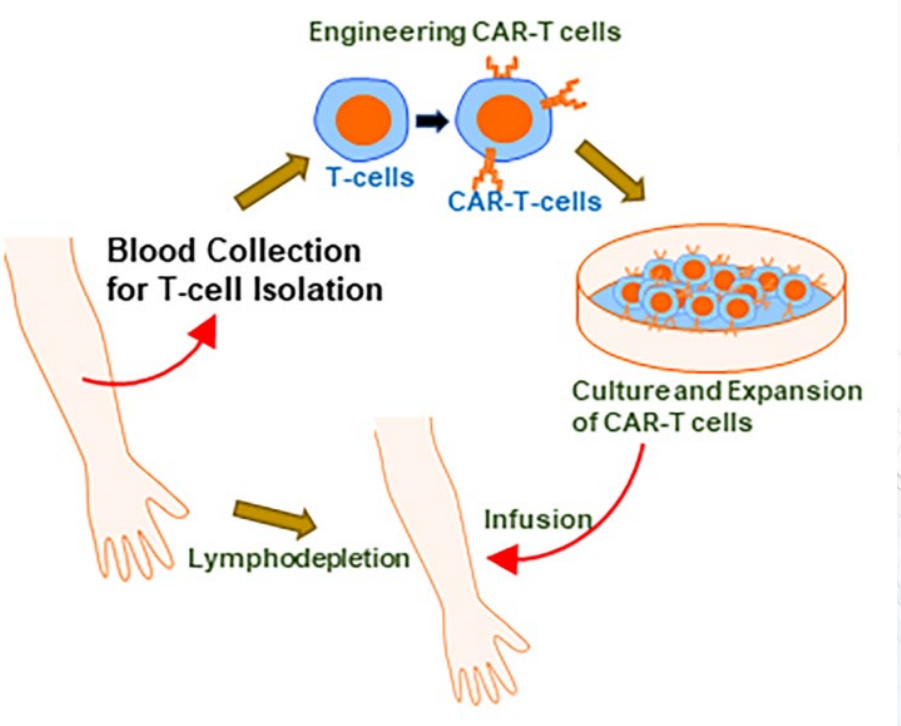
Introdução e Fundamento

Cátia Almeida

Complicações da terapia CAR-T

INTRODUÇÃO

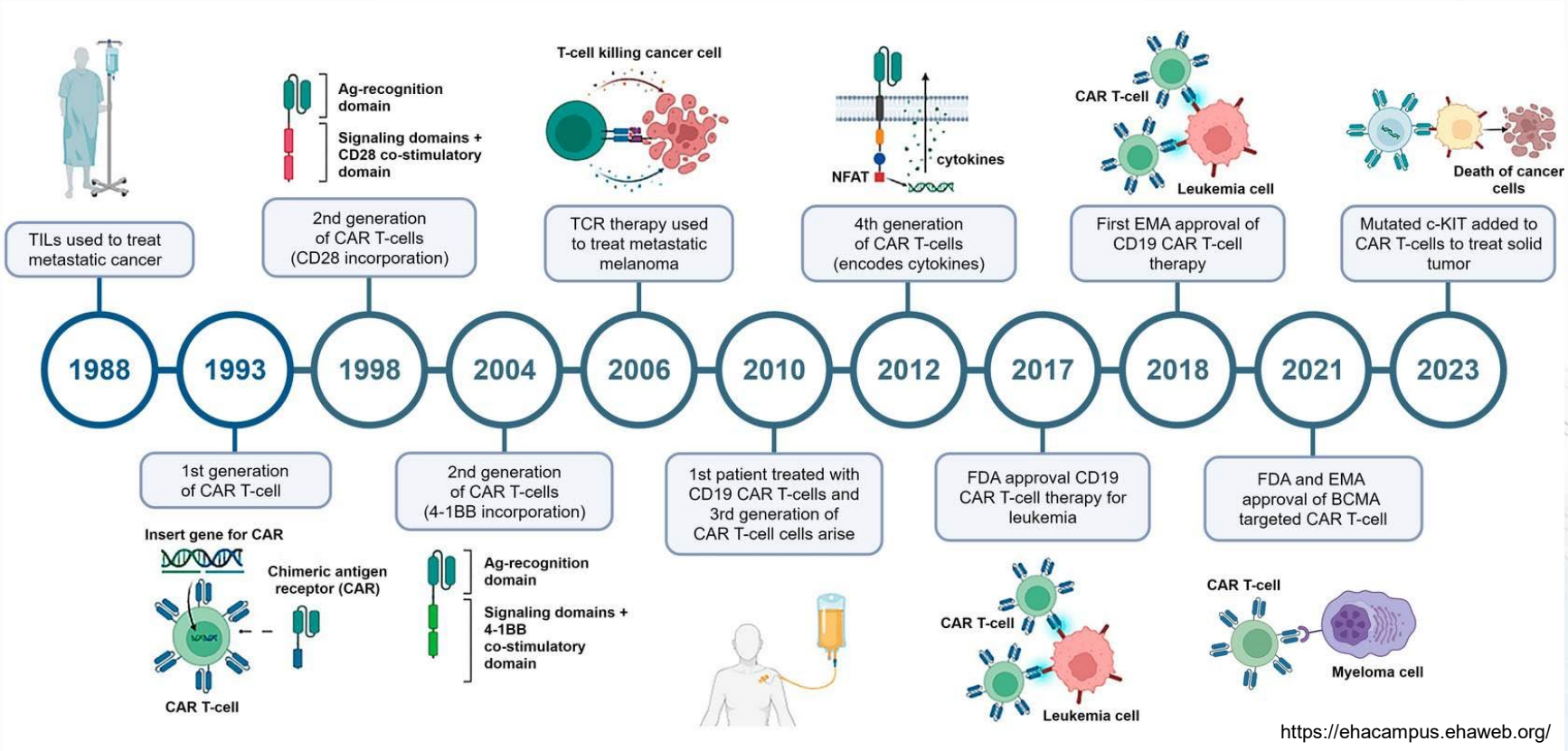
- Representa um grande avanço no tratamento de patologias hematológicas;
- Imunoterapia que modifica as células T do doente para expressarem a proteína CAR na sua superfície;
- Têm sido observadas elevadas taxas de resposta com esta terapêutica



Ahmar Aamid et al, 2020

Complicações da terapia CAR-T

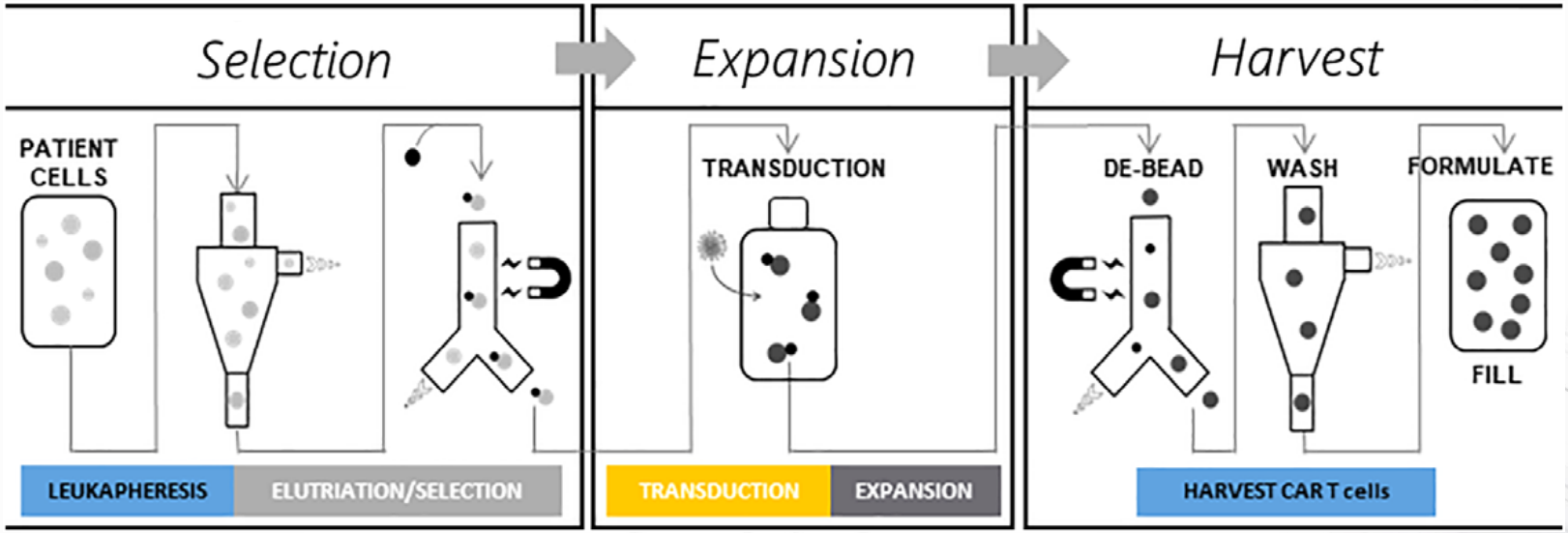
TERAPIA CART: EVOLUÇÃO HISTÓRICA



https://ehacampus.ehaweb.org/

Complicações da terapia CAR-T

TERAPIA CART: PROCESSO DE PRODUÇÃO



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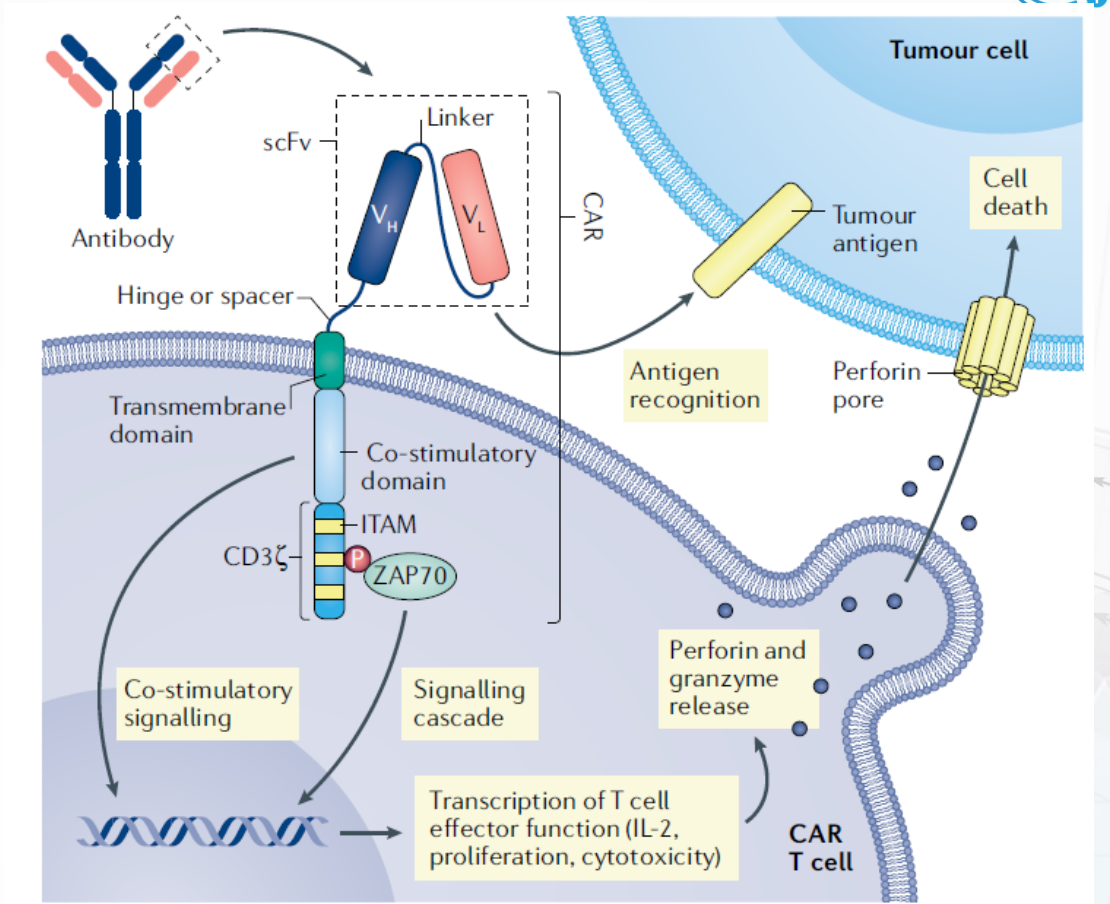
Feins, A. Et al, An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer, 2019

Complicações da terapia CAR-T

TERAPIA CART:
MECANISMO DE AÇÃO



Larson et al, 2021

Complicações da terapia CAR-T

TERAPIA CART: TERAPÊUTICAS APROVADAS

Commercial CAR T-cell therapy	Target	Indication	Date of EMA marketing authorization	Date of FDA marketing authorization
tisagenlecleucel/Kymriah®	CD19	Paediatric 3L+ ALL	September 2018 (EMA, 2021b)	August 2017 (FDA, 2021c)
		3L+ DLBCL	September 2018 (EMA, 2021b)	May 2018 (FDA, 2021c)
		3L+ HGBL	—	May 2018 (FDA, 2021c)
		3L+ DLBCL from FL	—	May 2018 (FDA, 2021c)
		3L+ FL	March 2022/positive CHMP opinion received (EMA, 2022c)	—
axicabtagene ciloleucel/Yescarta®	CD19	3L+ DLBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		2L+ DLBCL	—	April 2022 (FDA, 2022b)
		3L+ PMBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		3L+ HGBL	—	October 2017 (FDA, 2022c)
		3L+ DLBCL from FL	—	October 2017 (FDA, 2022c)
		4L+ FL (EMA)	April 2022/positive CHMP opinion received (EMA, 2022d)	April 2021 (FDA, 2022c)
		3L+ FL (FDA)		
brexucabtagene autoleucel/Tecartus®	CD19	3L+ MCL (EMA)	December 2020 (EMA, 2021c)	July 2020 (FDA, 2021d)
		2L+ MCL (FDA)		
		Adult 2L+ ALL	—	October 2021 (FDA, 2021d)
isocabtagene maraleucel/Breyanzi®	CD19	3L+ DLBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ PMBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ HGBL	—	February 2021 (FDA, 2021b)
		3L+ DLBCL from FL	—	February 2021 (FDA, 2021b)
		3L+ FL (grade 3B)	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
idecabtagene vicleucel/Abecma®	BCMA	4L+ MM (EMA)	August 2021 (EMA, 2021a)	March 2021 (FDA, 2021a)
		5L+ MM (FDA)		
ciltacabtagene autoleucel/Carvykti®	BCMA	4L+ MM (EMA)	March 2022/positive CHMP opinion received (EMA, 2022b)	February 2022 (FDA, 2022a)
		5L+ MM (FDA)		

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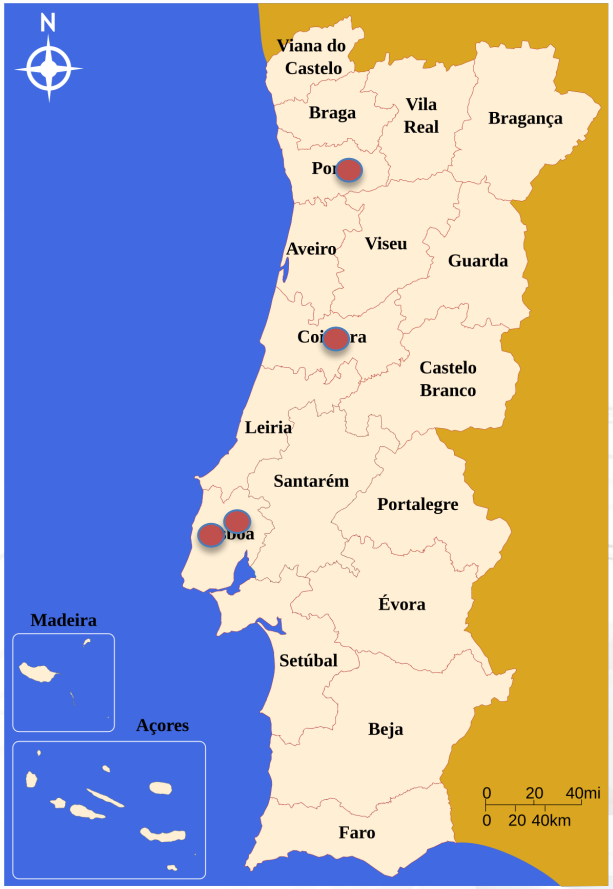
Jommi et al, 2022

Complicações da terapia CAR-T

TERAPIA CART: E EM PORTUGAL?

- IPO Porto
- ULS Coimbra
- ULS Santa Maria
- IPO Lisboa



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Complicações Imunológicas Precoces

André Antunes

Complicações Imunológicas Precoces

Síndrome de Libertação de Citocinas

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

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➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Dose de CAR-T
- Idade
- Carga Tumoral
- Infeção concomitante
- Hipofosfatémia

	Grau 1-2	Grau ≥3
Axi-cel	90% (76 – 100%)	7% (6 – 11%)
Tisa-cel	57% (49 – 61%)	6% (0 – 23%)
Liso-cel	43% (36 – 60%)	1% (1– 2%)
Brexu-cel	91%	15%
Cilta-cel	95%	5%
Ide-cel	88%	5%

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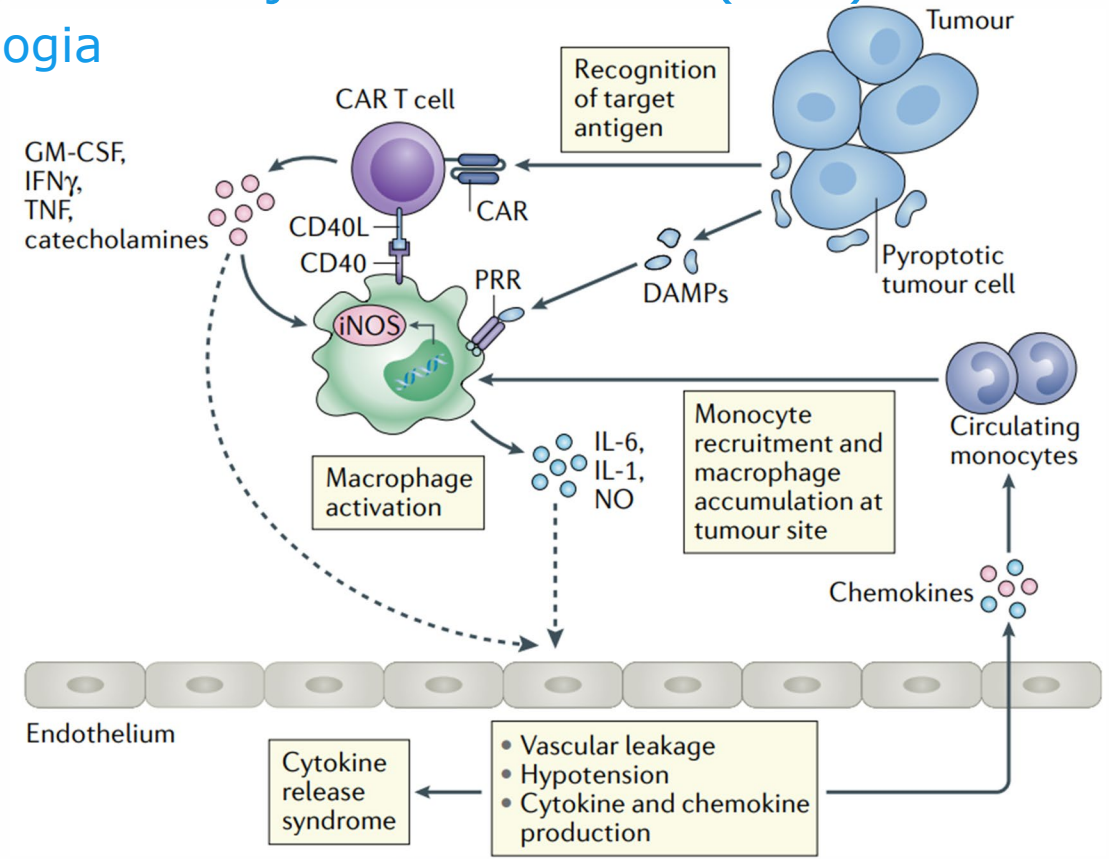
Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

- Fisiopatologia



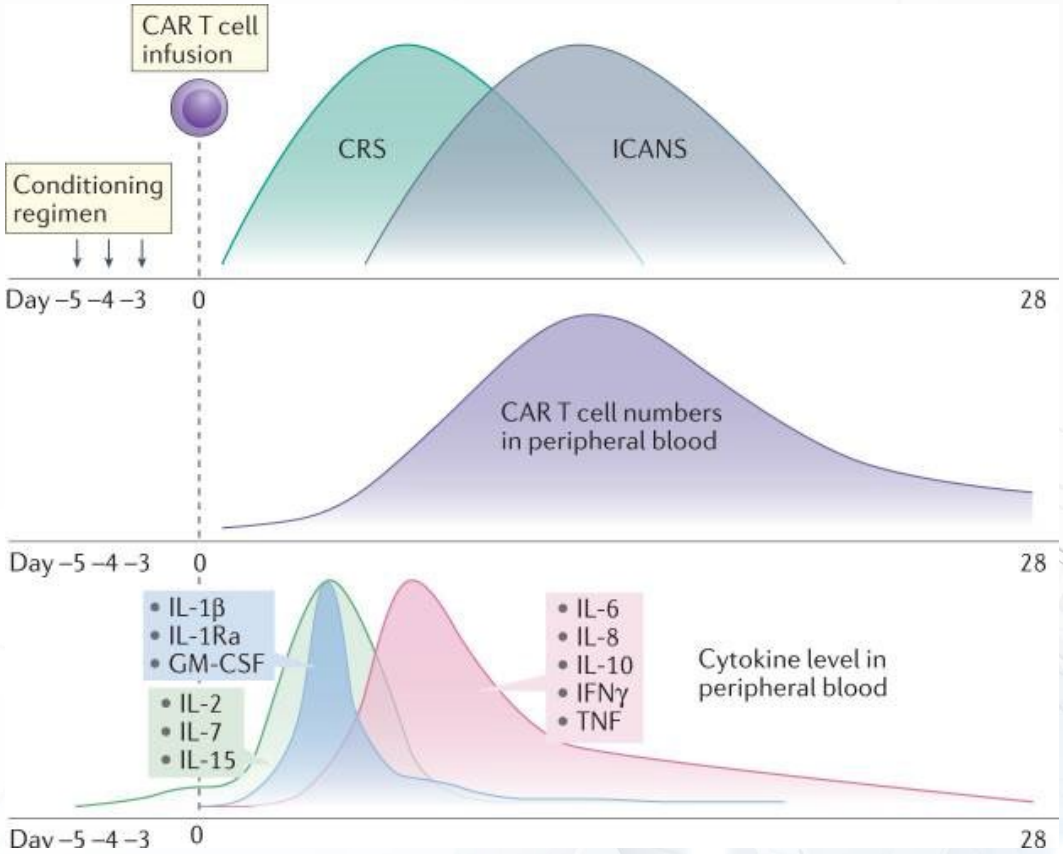
Morris, Emma C et al. "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy." *Nature reviews. Immunology* vol. 22,2 (2022)

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

➢ Abordagem Diagnóstica

- Início: D+1 a D+14 (Mediana D+3)
- Duração: 1 – 10 dias (Mediana 4 dias)



Morris, Emma C et al. "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy." *Nature reviews. Immunology* vol. 22,2 (2022)

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas (CRS)

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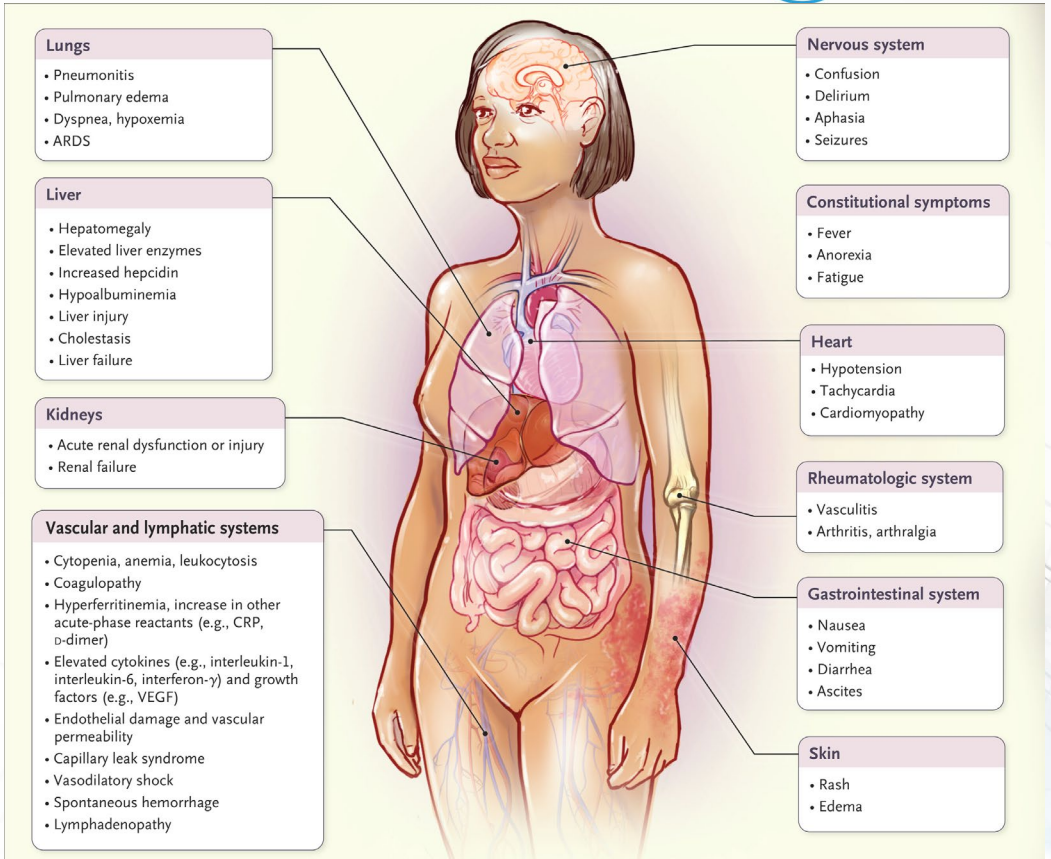
➢ Abordagem Diagnóstica

- Febre
- Sintomas constitucionais
- Instabilidade hemodinâmica
- Hipóxia

⚠ Diagnóstico de exclusão



Fajgenbaum, David C, and Carl H June. "Cytokine Storm." *The New England journal of medicine* vol. 383,23 (2020)

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Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

- Abordagem Diagnóstica

Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

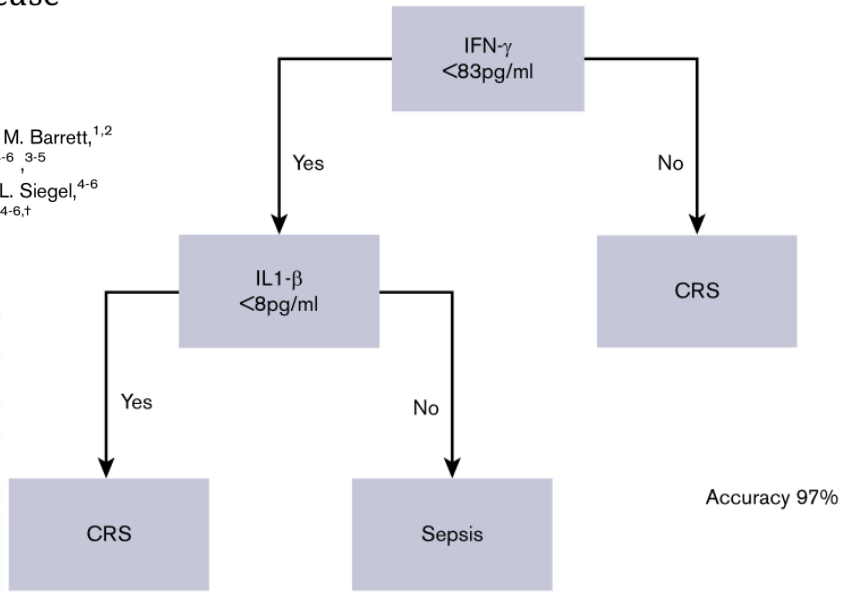
➢ Abordagem Diagnóstica

REGULAR ARTICLE

blood advances

Diagnostic biomarkers to differentiate sepsis from cytokine release syndrome in critically ill children

Caroline Diorio,[1,2,*] Pamela A. Shaw,[3,*] Edward Pequignot,[4] Alena Orlenko,[3] Fang Chen,[4-6] Richard Aplenc,[1,2,5] David M. Barrett,[1,2] Hamid Bassiri,[7] Edward Behrens,[2,8] Amanda M. DiNofia,[1,2] Vanessa Gonzalez,[4-6] Natalka Koterba,[4-6] Bruce L. Levine,[4-6,3-5] Shannon L. Maude,[1,2] Nuala J. Meyer,[9] Jason H. Moore,[3] Michele Paessler,[6] David L. Porter,[5,10] Jenny L. Bush,[11] Don L. Siegel,[4-6] Megan M. Davis,[4] Donglan Zhang,[11] Carl H. June,[4-6] Stephan A. Grupp,[1,2,5] J. Joseph Melenhorst,[4-6,†] Simon F. Lacey,[4-6,†] Scott L. Weiss,[11-14,†] and David T. Teachey[1,2,5,†]



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Complicações da terapia CAR-T

Síndrome de Libertação de Citocinas

➢ Graduação (ASTCT)

Grau 1

Febre
+
Sem Hipotensão
+
Sem Hipoxemia

Grau 2

Febre
+
Hipotensão sem necessidade de vasopressores
±
Hipoxemia com necessidade de O2 por óculos nasais ≤6L/min

Grau 3

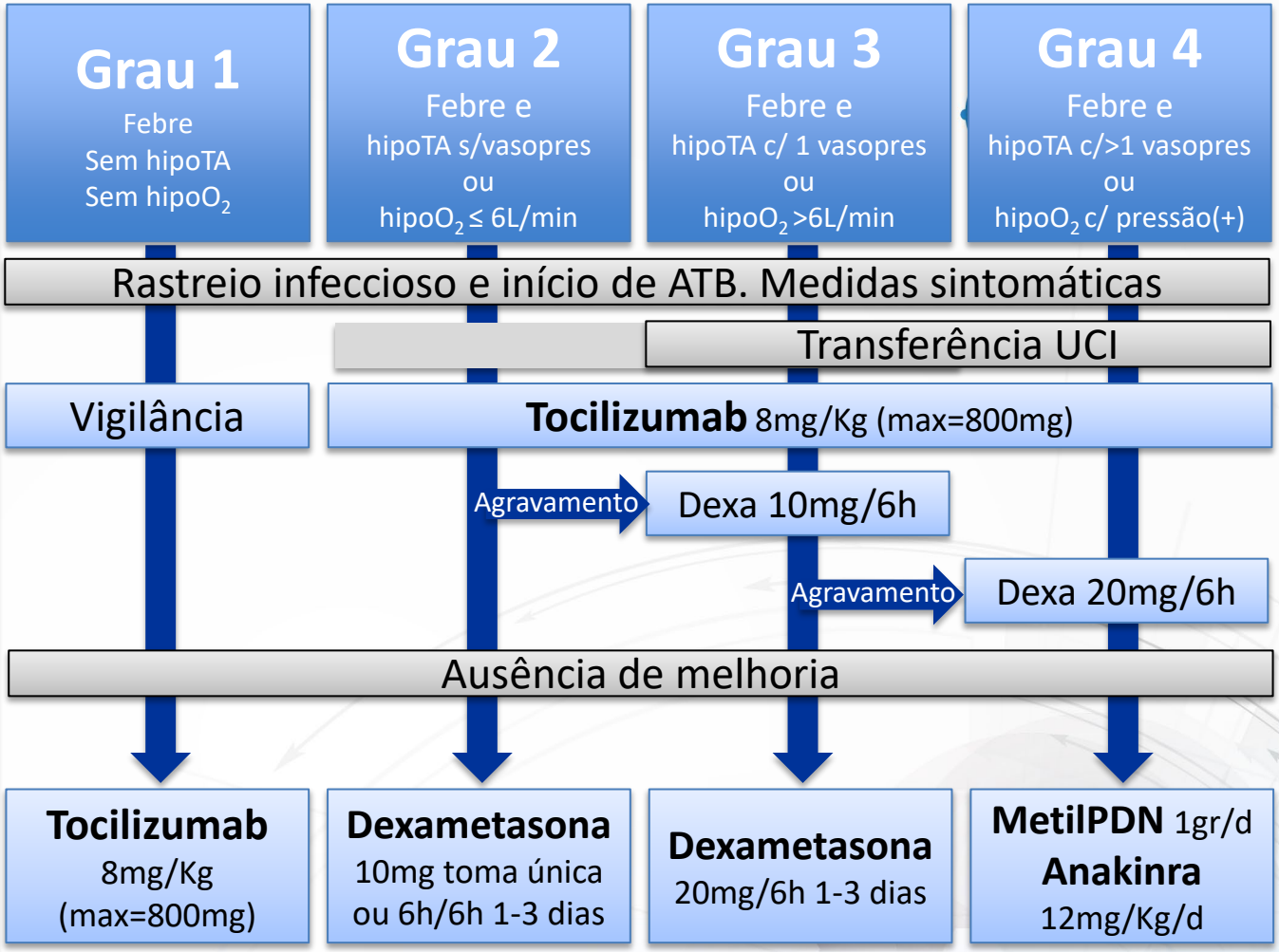
Febre
+
Hipotensão com necessidade de 1 vasopressor
±
Hipoxemia com necessidade de O2 por masc. facial, Venturi, *High-Flow*

Grau 4

Febre
+
Hipotensão com necessidade de ≥1 vasopressor (exclui vasipressina)
±
Hipoxemia com necessidade de O2 com pressão positiva (CPAP, BiPAP, VMI)

Complicações da terapia CAR-T
CRS

- Abordagem Terapêutica



Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
CRS

- Abordagem Terapêutica

Complicações Imunológicas Precoces

Síndrome de Ativação Macrofágica

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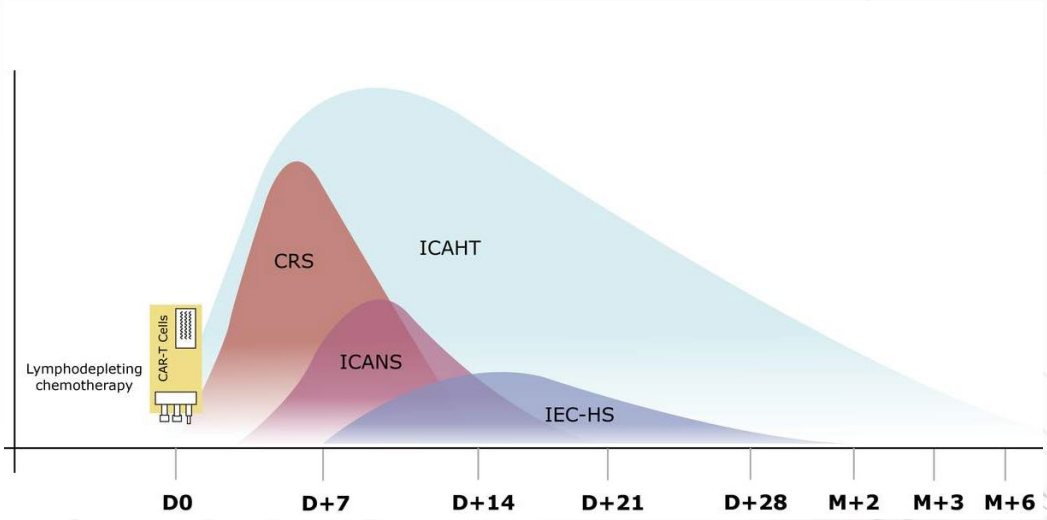
Complicações da terapia CAR-T
Síndrome de Ativação Macrofágica (IEC-HS)

- Complicação rara mas grave
- Inicio variável

- Síndrome hiperinflamatório sistémico
- Ativação de macrófagos e linfócitos, hemofagocitose e lesão multiorgânica



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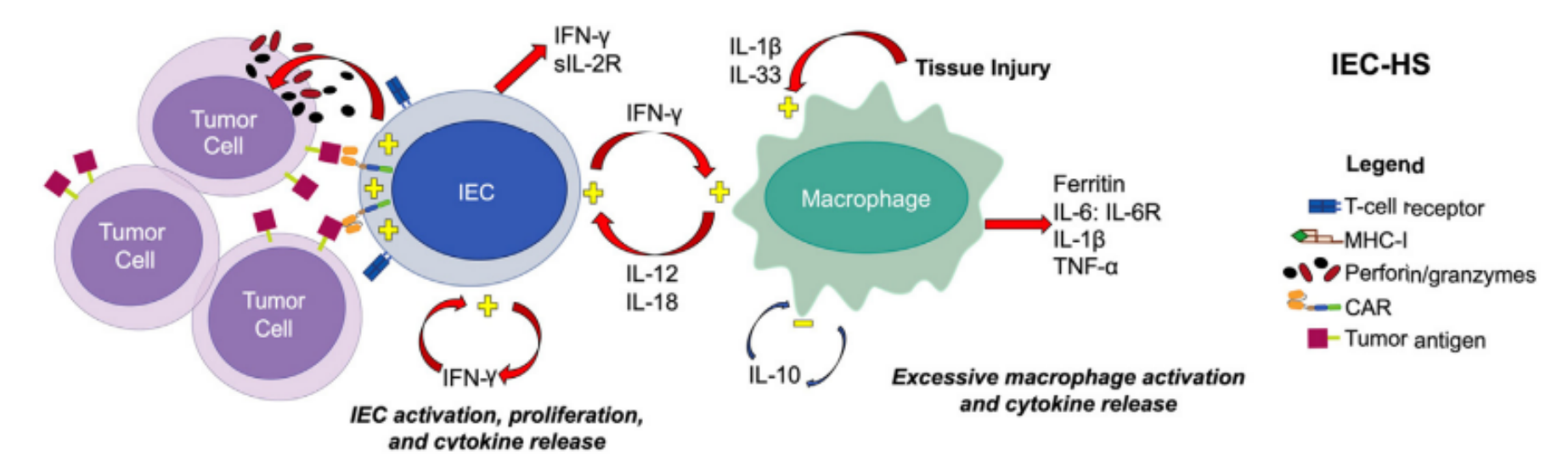
Hines, Melissa R et al. “Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome.” *Transplantation and cellular therapy* vol. 29,7 (2023)

Complicações da terapia CAR-T

Síndrome de Ativação Macrofágica (IEC-HS)

➢ Fisiopatologia



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Hines, Melissa R et al. "Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome." *Transplantation and cellular therapy* vol. 29,7 (2023)

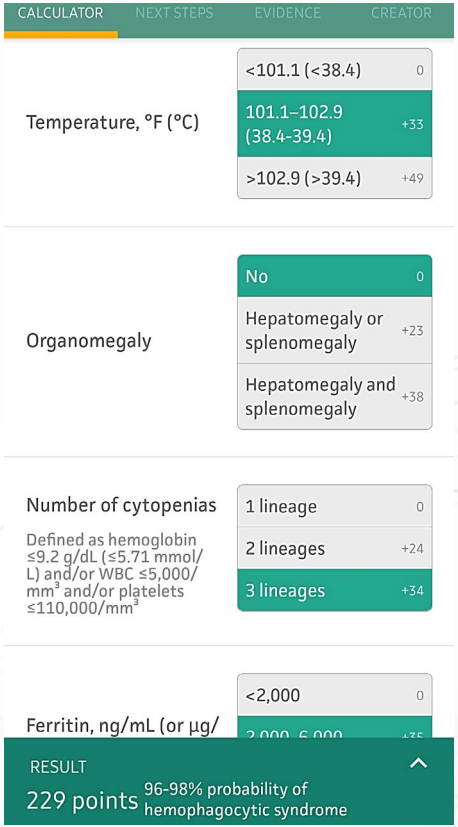
Complicações da terapia CAR-T

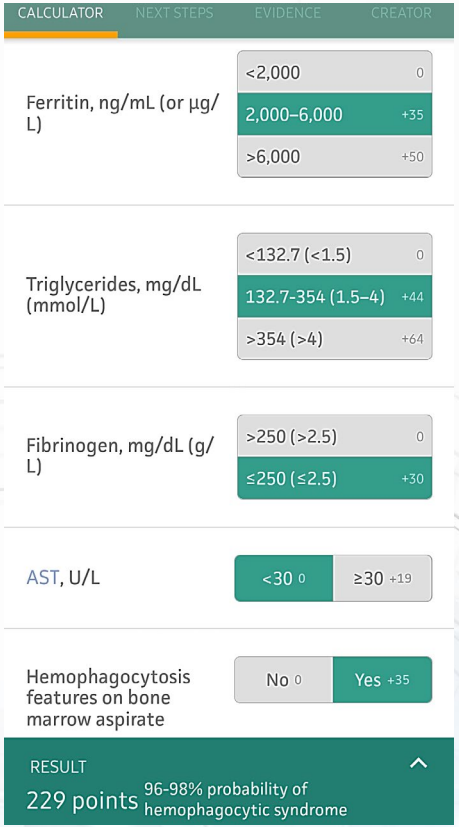
Síndrome de Ativação Macrofágica

➢ Abordagem Diagnóstica

Pelo menos 5 de:

- Febre
- Esplenomegalia
- Citopénia ≥2
- Hipertrigliceridémia (≥3 mmol/L) ou Hipofibrinogenémia (<1.5 g/L)
- ↑ Ferritina (≥500 µg/L)
- ↑ sCD25 (≥2.400 U/ml
- ↓ Actividade linf NK
- Hemafagocitose





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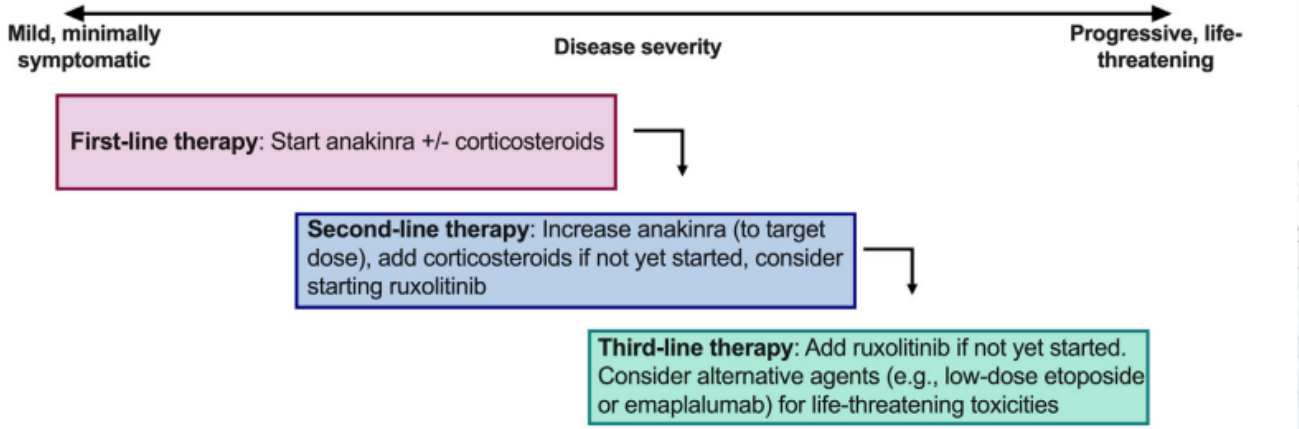
Complicações da terapia CAR-T
MAS

- Abordagem Terapêutica

Monitoring	
• Daily monitoring of complete blood cell count with differential and coagulation parameters (PT/PTT) and fibrinogen • Frequent (eg, daily) evaluation for renal and hepatic dysfunction • Assessment for bacterial, viral reactivation or new infection, and fungal disease, in blood, urine, and sputum cultures, with or without sampling of other possible infectious sources (eg, bronchoscopy, cerebrospinal fluid), • Consider testing for HLH diagnostic parameters, including soluble CD25, NK cell function, triglycerides, IFN-γ, CXCL9 ratio, CXCL10, IL-10, and IL-18	
Cytopenias and coagulopathy	
Cytopenias	• Maintain hemoglobin $\geq$7 g/dL [147,148]. • Platelet count $\geq$50 cells $\times$ 10^9/L is recommended in those with active bleeding or coagulopathy. • Use of romiplostim or eltrombopag is unknown. • Use of G-CSF to maintain an absolute neutrophil count $\geq$500 cells/mm^3 remains controversial during periods of active inflammation [132–135]. • Consult gynecology in female patients with menorrhagia
Coagulopathy	• Aggressive management with cryoprecipitate or fibrinogen concentrate is recommended to keep fibrinogen level >100 if no bleeding and >150 if bleeding is present [140]. • If INR is >1.5, then vitamin K supplementation should be considered. If INR is >2, then administration of fresh frozen plasma in addition to cryoprecipitate should be considered. • Use of agents for prevention of venous thromboembolism should be used with caution with preference for agents that are easily reversed (ie, heparin). • Consult hematology for patients with refractory or difficult to manage coagulopathy.



Hines, Melissa R et al. "Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome." *Transplantation and cellular therapy* vol. 29,7 (2023)

Complicações Imunológicas Precoces

Immune effector cell-associated neurotoxicity syndrome

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Complicações da terapia CAR-T
ICANS

➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Idade
- Doença neurológica prévia
- Carga tumoral
- CRS precoce e severo
- Trombocitopénia
- Estado inflamatório pré-infusão
- Neurofilament Light Chain

	Grau 1-2	Grau ≥3
Axi-cel	51% (59 – 72%)	19% (19 – 32%)
Tisa-cel	28% (10 – 37%)	6% (2 – 11%)
Liso-cel	22% (12 – 31%)	6% (4 – 10%)
Brexu-cel	63%	19%
Cilta-cel	22%	12%
Ide-cel	15%	3%

Complicações da terapia CAR-T
ICANS

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➢ Prevalência e Factores de Risco

- Tipo de CAR-T
- Idade
- Doença neurológica prévia
- Carga tumoral
- CRS precoce e severo
- Trombocitopénia
- Estado inflamatório pré-infus
- Neurofilament Light Chain

JAMA Oncology | Brief Report

Assessment of Pretreatment and Posttreatment Evolution of Neurofilament Light Chain Levels in Patients Who Develop Immune Effector Cell–Associated Neurotoxicity Syndrome

Omar H. Butt, MD, PhD; Alice Y. Zhou, MD, PhD; Paolo F. Caimi, MD; Patrick H. Luckett, PhD; Julie K. Wisch, PhD; Paul-Robert Derenoncourt, MD; Kenneth Lee, BS; Gregory F. Wu, MD, PhD; Marcos J. G. de Lima, MD; Jian L. Campian, MD, PhD; Matthew J. Frank, MD, PhD; John F. DiPersio, MD, PhD; Armin Ghobadi, MD; Beau M. Ances, MD, PhD

Supplemental content

IMPORTANCE Determining whether neurofilament light chain (NfL) elevations in patients who develop immune effector cell–associated neurotoxicity syndrome (ICANS) occur before or after infusion of cellular product is important to identify high-risk patients and inform whether neuroaxonal injury is latent or a consequence of treatment.

OBJECTIVE To quantify serial NfL levels in patients undergoing cellular therapy.

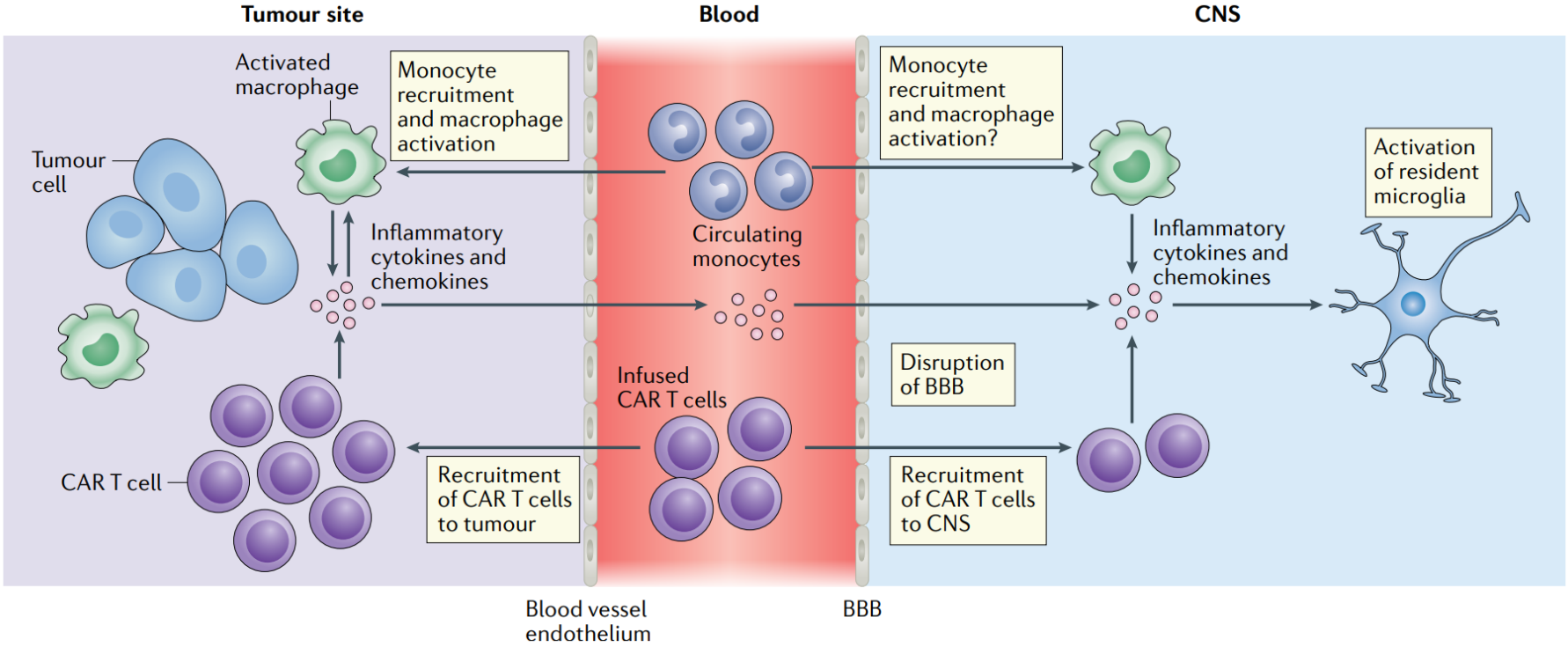
DESIGN, SETTING, AND PARTICIPANTS This retrospective 2-center study examined plasma NfL levels in 30 patients with detailed medical and treatment history, including all major pretreatment and posttreatment risk factors. Exclusion criteria included dementia and severe, symptomatic central nervous system (CNS) involvement.

MAIN OUTCOMES AND MEASURES Patients' NfL levels were measured at 7 time points: baseline (prelymphodepletion), during lymphodepletion, postinfusion day (D) 1, D3, D7, D14, and D30. Prediction accuracy for the development of ICANS was next modeled using receiver operating characteristic (ROC) classification. Finally, univariate and multivariate modeling examined the association between NfL levels, ICANS, and potential risk factors including demographic (age, sex), oncologic (tumor burden, history of CNS involvement), neurologic (history of nononcologic CNS disease or neuropathy), and neurotoxic exposure histories (vincristine, cytarabine, methotrexate, or CNS radiotherapy).

Complicações da terapia CAR-T

ICANS

➢ Fisiopatologia



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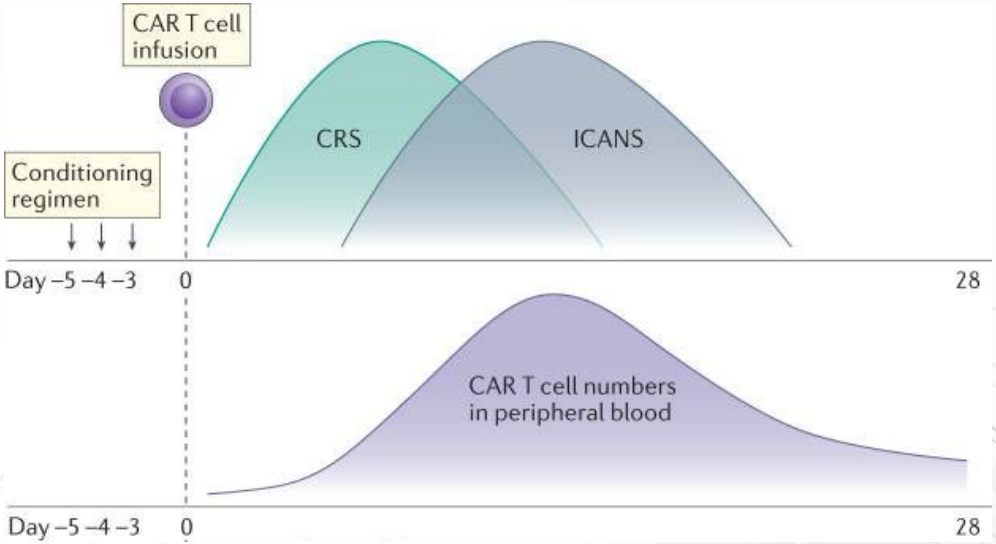
Morris, E.C., Neelapu, S.S., Giavridis, T. *et al.* Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* **22**, 85–96 (2022).

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Mediana inicio: D+6
  - Até 10% de ICANS tardio
- Mediana duração: 8 dias



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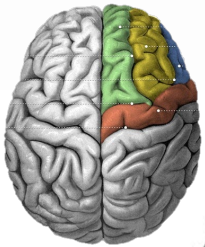
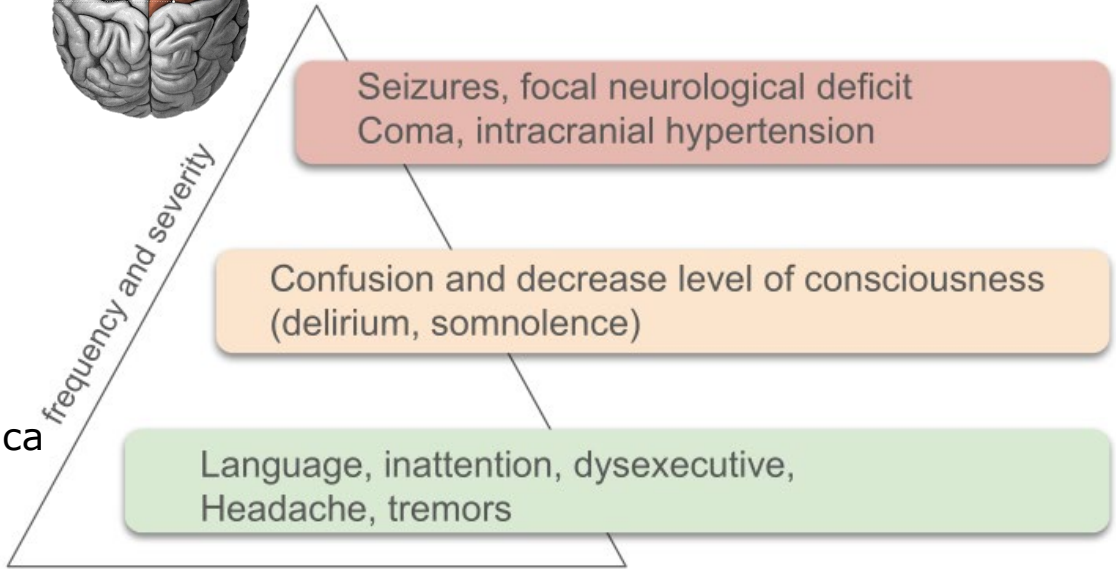
Morris, E.C., Neelapu, S.S., Giavridis, T. *et al.* Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* **22**, 85–96 (2022).

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
  - Atividade paroxística
- RMN
  - Edema focal/generalizado
  - Hemorragias punctiformes
  - ↑ Realce leptomeníngeo
  - ↑ Intensidade FLAIR s. branca
- Punção Lombar





Complicações da terapia CAR-T

ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
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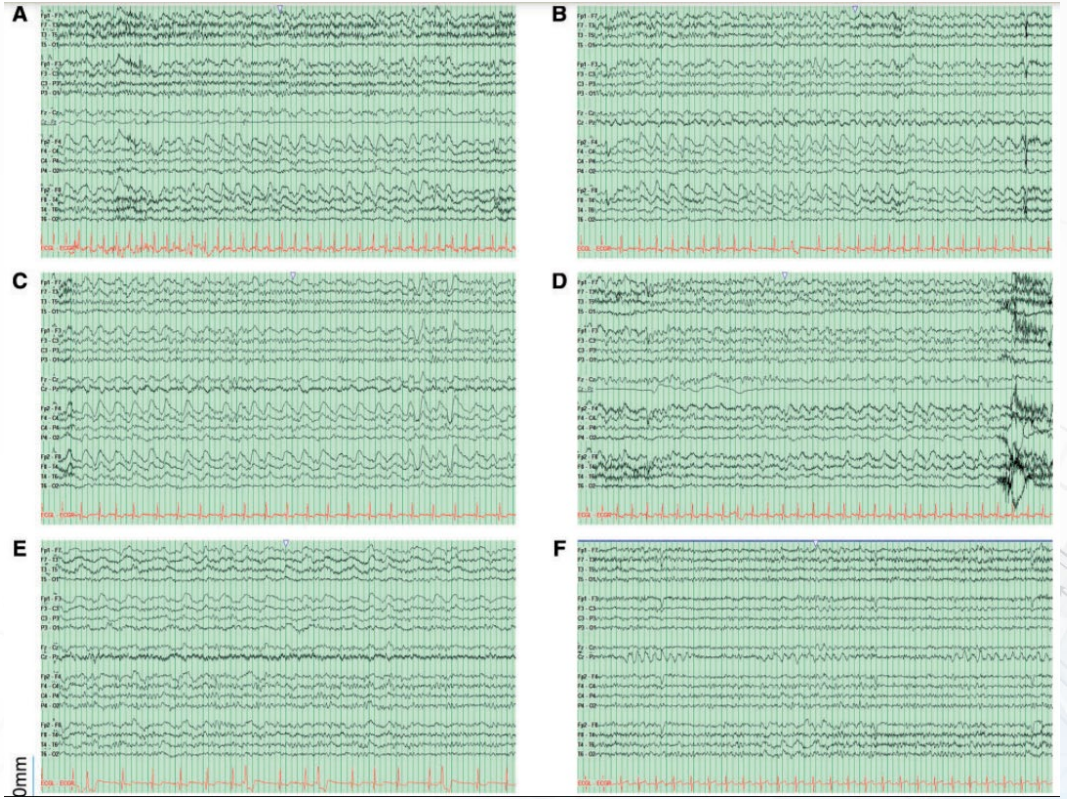
- Punção Lombar



Daniel B Rubin et all, Neurological toxicities associated with chimeric antigen receptor T-cell therapy, *Brain*, May 2019

Complicações da terapia CAR-T
ICANS

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➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
  - Atividade paroxística
- RMN
  - Edema focal/generalizado
  - Hemorragias punctiformes
  - ↑ Realce leptomeníngeo
  - ↑ Intensidade FLAIR s. branca
- Punção Lombar

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REGULAR ARTICLE

blood advances

Check for upda

Impact of diagnostic investigations in the management of CAR T-cell–associated neurotoxicity

Matteo Mauget,[1,2] Sophie Lemercier,[3] Quentin Quelven,[2] Adel Maamar,[2] Faustine Lhomme,[1] Sophie De Guibert,[1] Roch Houot,[1,4] and Guillaume Manson[1]

[1]Department of Hematology, [2]Department of Infectious Diseases and Intensive Care Unit, and [3]Department of Neurology, University Hospital of Rennes, Rennes, France; and [4]INSERM, U1236, Rennes, France

Key Points

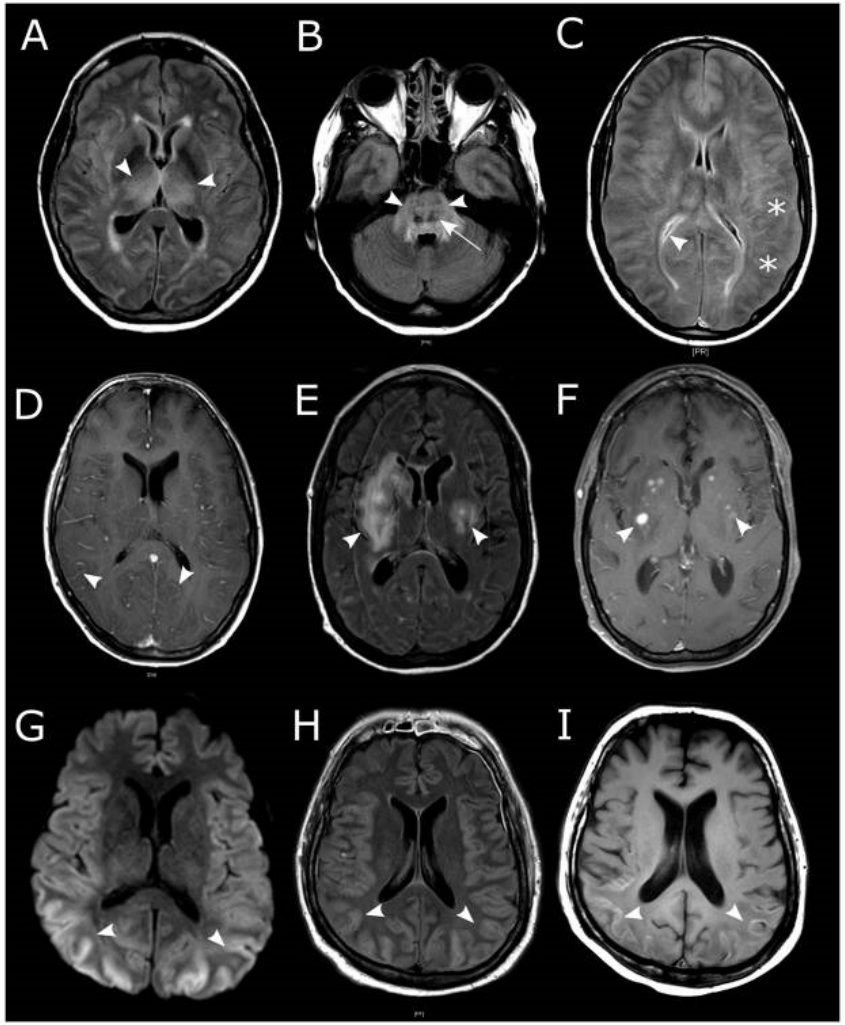
- Data from a large cohort of CAR T-cell–treated patients question guidelines regarding diagnostic investigations in ICANS management.
- Our results emphazise for the first time the role of EEG in the current guidelines but questions the need for systematic MRI and LP.

International guidelines regarding the management of immune effector cell–associated neurotoxicity syndrome (ICANS) recommend several diagnostic investigations, including magnetic resonance imaging (MRI), lumbar puncture (LP), and electroencephalogram (EEG) based on ICANS grade. However, the impact of these investigations has not yet been evaluated. Here, we aimed to describe the role of MRI, LP, and EEG in the management of ICANS in a cohort of real-life patients treated with chimeric antigen receptor (CAR) T cells at the University Hospital of Rennes, France. Between August 2018 and January 2023, a total of 190 consecutive patients were treated with CAR T cells. Among those, 91 (48%) developed ICANS. MRI was performed in 71 patients (78%) with ICANS, with a therapeutic impact in 4% of patients, despite frequent abnormal findings. LP was performed in 43 patients (47%), which led to preemptive antimicrobial agents in 7% of patients, although no infection was eventually detected. Systematic EEG was performed in 51 patients (56%), which led to therapeutic modifications in 16% of patients. Our study shows that EEG is the diagnostic investigation with the greatest therapeutic impact, whereas MRI and LP appear to have a limited therapeutic impact. Our results emphasize the role of EEG in the current guidelines but question the need for systematic MRI and LP, which might be left to the discretion of the treating physician.

Complicações da terapia CAR-T
ICANS

➢ Abordagem Diagnóstica

- Clínica
  - **Encefalopatia frontal**
- Eletroencefalograma
  - Atividade de base lenta
  - Atividade paroxística
- RMN
  - Edema focal/generalizado
  - Hemorragias punctiformes
  - ↑ Realce leptomeníngeo
  - ↑ Intensidade FLAIR s. branca
- Punção Lombar



Johnson&Johnson
Innovative Medicine

Gust, Juliane et al. "Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells." *Cancer discovery* vol. 7,12 (2017)

Complicações da terapia CAR-T

ICANS

➢ Graduação

***Score* ICE** (Immune Effector Cell Encephalopathy)

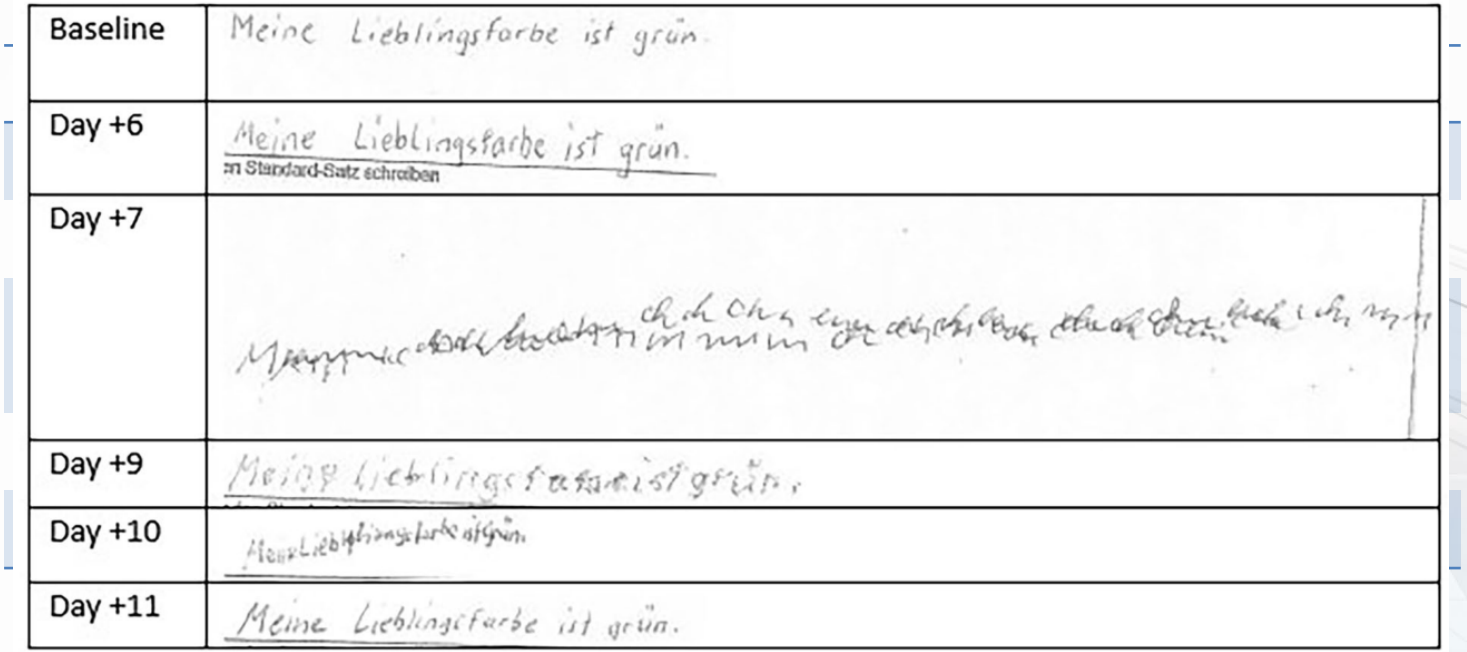
Teste	Pontuação
Orientação: Orientação no ano, mês, cidade, hospital	4
Nomeação: Capacidade de nomear 3 objetos	3
Cumprimento de ordens: Capacidade de seguir ordens simples (“sorrir”, “tocar com 3 dedos na testa”)	1
Escrita: Capacidade de escrever uma frase *standart*	1
Atenção: Capacidade de contar de 100 até 0, de 10 em 10	1

Complicações da terapia CAR-T

ICANS

- Graduação

***Score* ICE** (Immune Effector Cell Encephalopathy)



Baseline	Meine Lieblingsfarbe ist grün.
Day +6	Meine Lieblingsfarbe ist grün. (in Standard-Satz schreiben)
Day +7	
Day +9	
Day +10	
Day +11	Meine Lieblingsfarbe ist grün.

Johnson&Johnson Innovative Medicine

Schroeder, Torsten et al. "Management of chimeric antigen receptor T (CAR-T) cell-associated toxicities." *Intensive care medicine* vol. 50,9 (2024)

Complicações da terapia CAR-T

ICANS

➢ Graduação

***Score* ICE** (Immune Effector Cell Encephalopathy)

Teste	Pontuação
Orientação: Orientação no ano, mês, cidade, hospital	4
Nomeação: Capacidade de nomear 3 objetos	3
Cumprimento de ordens: Capacidade de seguir ordens simples (“sorrir”, “tocar com 3 dedos na testa”)	1
Escrita: Capacidade de escrever uma frase *standart*	1
Atenção: Capacidade de contar de 100 até 0, de 10 em 10	1

Complicações da terapia CAR-T

ICANS

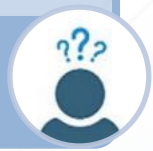
➢ Graduação

Grau 1

- ICE 7-9
- Diminuição do nível de consciência: Despertar espontâneo

Grau 2

- ICE 3-6
- Diminuição do nível de consciência: Despertar à voz

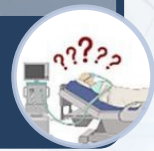


Grau 3

- ICE 0-2
- Diminuição do nível de consciência: Despertar a estimulo táctil
- Edema focal em exame de imagem
- Convulsão/Actividade epilética com resolução rápida

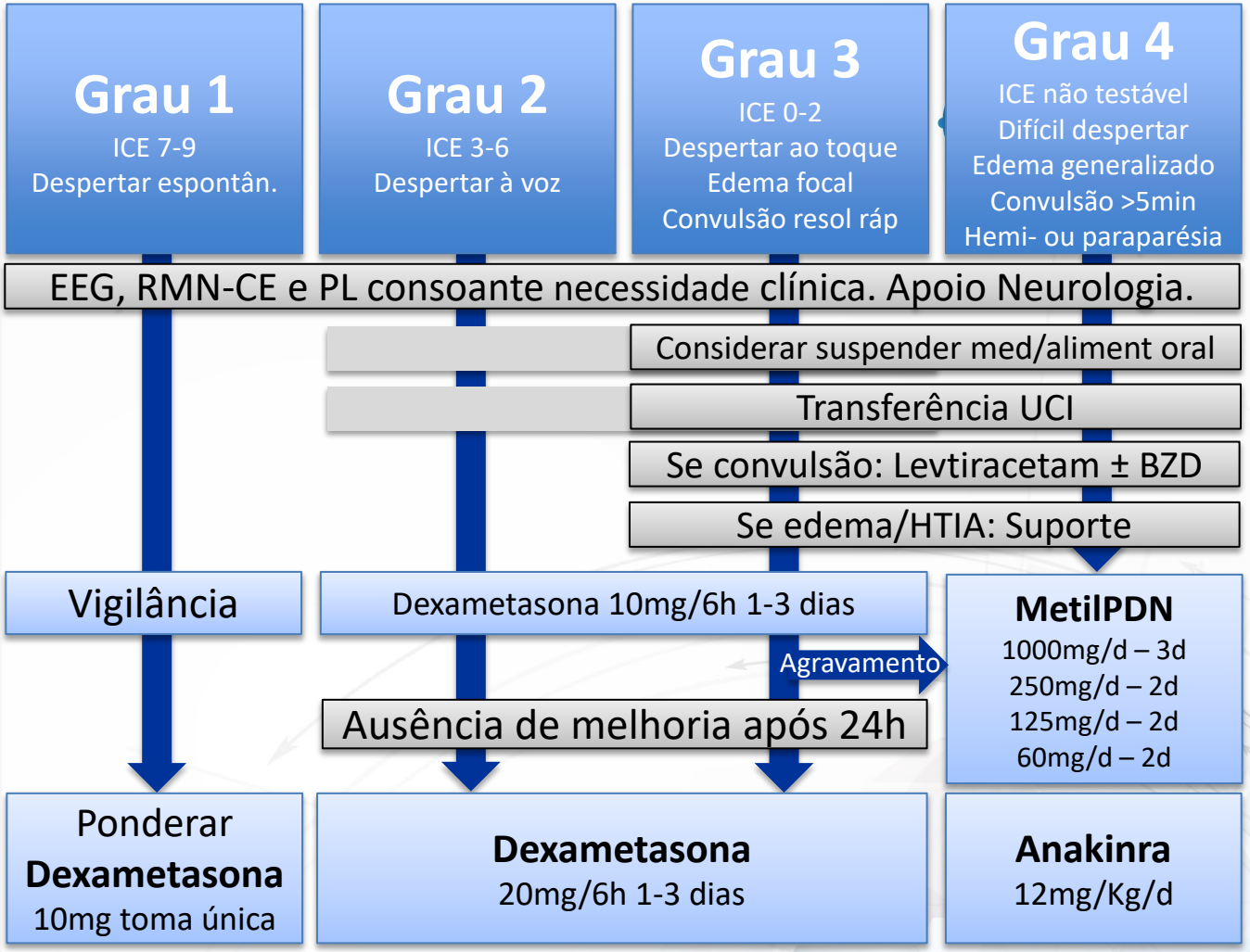
Grau 4

- ICE 0
- Despertar a estimulo vigoroso ou não despertável
- Edema generalizado em exame de imagem
- Postura descorticada, paralisia VI, edema papilar, Triade Cusching
- Convulsão prolongada (>5min)
- Défices motores focais



Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica



Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica

- Abordagem **ABC**
- **Levtiracetam 1500mg** e.v. + escalar manutenção
- **Diazepam 0.15mg/Kg (max 10mg)** ou Midazolam 5mg ou Lorazepam 0.5mg.
- **Dexametasona** 20mg/6h

- <u>Se refratário:</u> **Propofol** (bólus 2mg/Kg → per. 10mg/Kg/h) ± **Midazolam** (bólus 0.2mg/kg → perf. 0.1-0.5mg/Kg/h)

Grau 1
ICE 7-9
Despertar espontân.

Grau 2
ICE 3-6
Despertar à voz

Grau 3
ICE 0-2
Despertar ao toque
Edema focal
Convulsão resol ráp

Grau 4
ICE não testável
Difícil despertar
Edema generalizado
Convulsão >5min
Hemi- ou paraparésia

ecessidade clínica. Apoio Neurologia.

Considerar suspender med/aliment oral

Transferência UCI

Se convulsão: Levtiracetam ± BZD

Se edema/HTIA: Suporte

a 10mg/6h 1-3 dias

Agravamento

melhoria após 24h

MetilPDN
1000mg/d – 3d
250mg/d – 2d
125mg/d – 2d
60mg/d – 2d

ametasona
ng/6h 1-3 dias

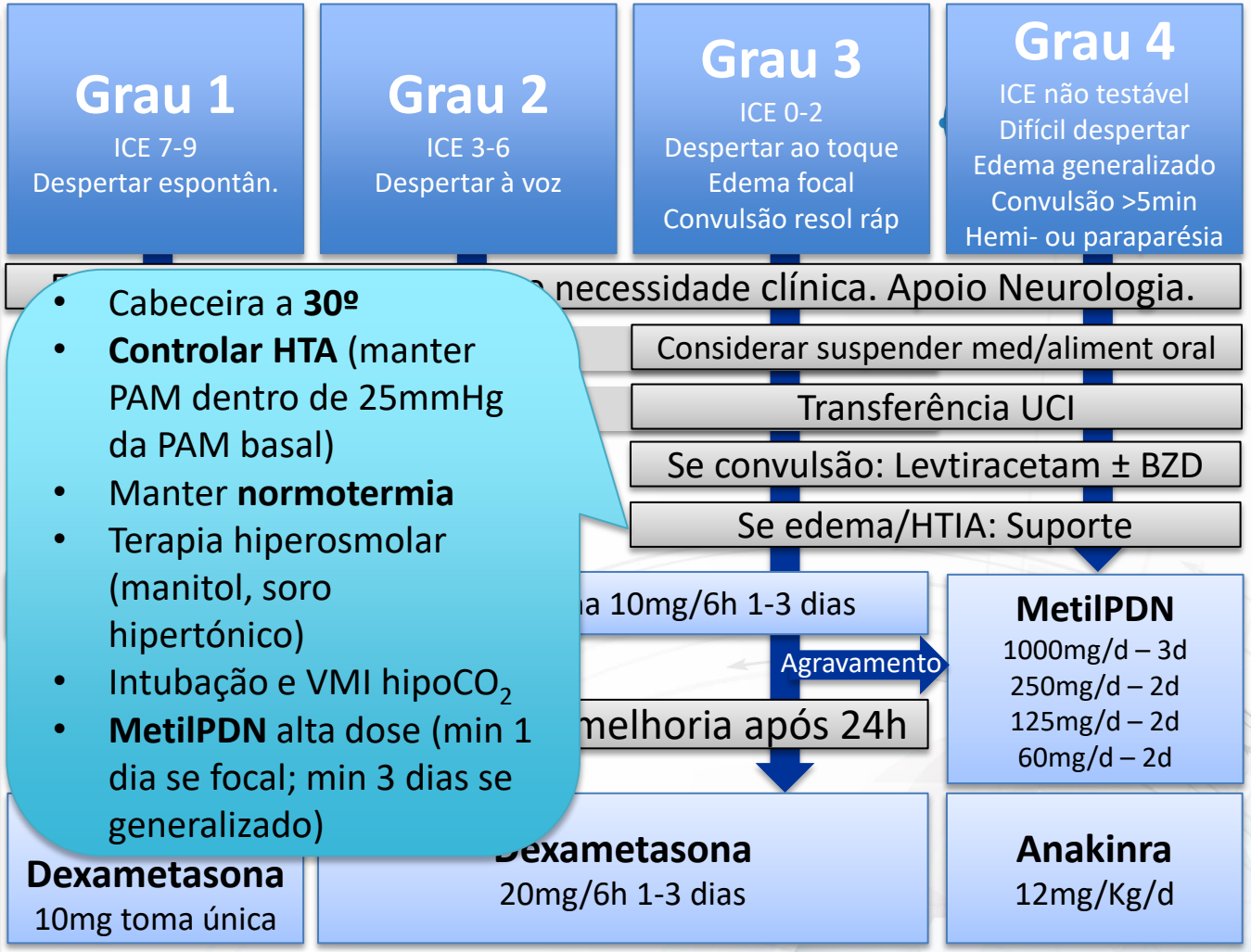
Anakinra
12mg/Kg/d

10mg toma única

Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica



- Cabeceira a **30º**
- **Controlar HTA** (manter PAM dentro de 25mmHg da PAM basal)
- Manter **normotermia**
- Terapia hiperosmolar (manitol, soro hipertónico)
- Intubação e VMI hipoCO_2
- **MetilPDN** alta dose (min 1 dia se focal; min 3 dias se generalizado)

Adaptado de Hayden, P J et al. "Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)." *Annals of oncology : official journal of the European Society for Medical Oncology* vol. 33,3 (2022)

Complicações da terapia CAR-T
ICANS

- Abordagem Terapêutica

Complicações da terapia CAR-T
Outras Toxicidades Neurológicas

➢ Tumor Inflammation Associated Neurotoxicity (TIAN)

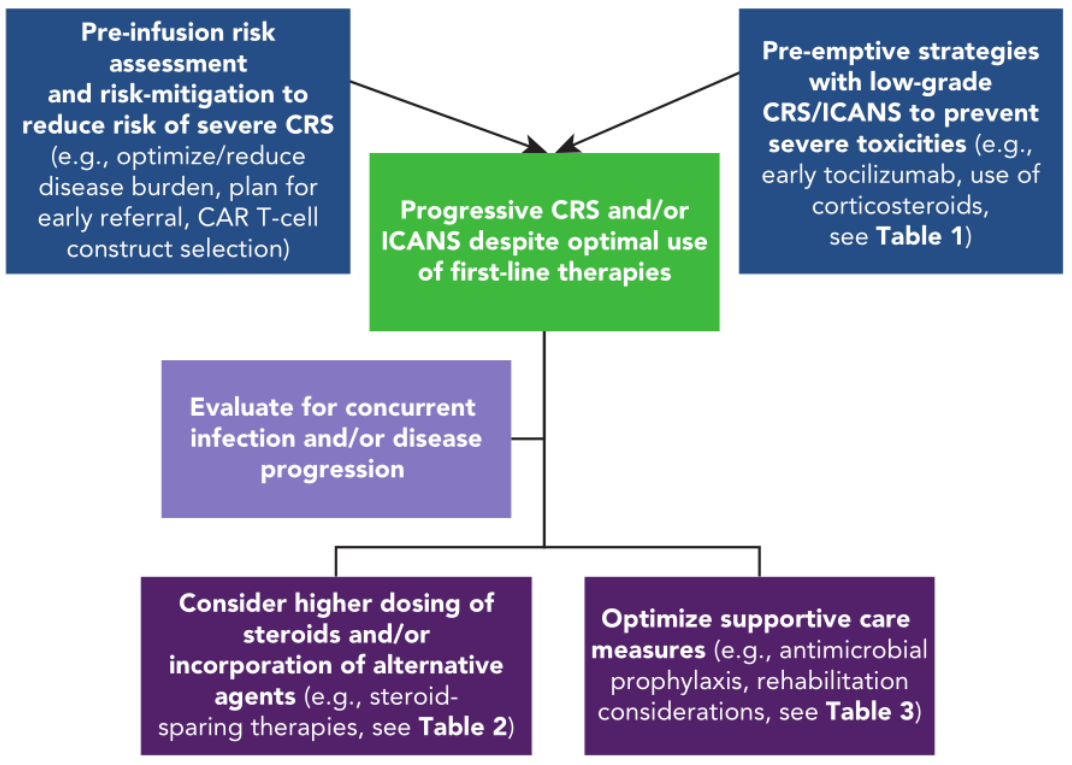
- Doentes com doença SNC+
- *Tumour flare*
- Hipertensão intracraniana, convulsões, etc
- Imagiologia característica

➢ Perturbação neurocognitiva e hipocinética dos movimentos com caraterísticas de Parkinson

- CAR-T anti-BCMA
- Toxicidade *on target off tumor* – Gânglios da base
- Inicio mais tardio (D+27)
- Duração mais prolongada (75 dias)

Complicações da terapia CAR-T

Prevenção



Jain, Michael D et al. “How I treat refractory CRS and ICANS after CAR T-cell therapy.” *Blood* vol. 141,20 (2023)

Complicações da terapia CAR-T

Prevenção

Strategy	Disease/product	Outcome	Comparison*	Comments	Reference
Fractionated CAR T-cell dosing					
Fractionated dosing: day 1 (10% dose), day 2 (30%), and day 3 (60%), with day 2 and day 3 doses allowed to be held for early CRS.	Adult B-ALL treated with CD19 CAR T cells.	Fractionated dose: grade ≥4 CRS, 5% (Penn grading scale) Grade ≥3 neurotoxicity, 6%.	High fixed dose: grade ≥4 CRS, 50%; 3 of 6 patients died.	Difficult to implement with fixed-dose commercial CAR T-cell products.	Frey et al[25] NCT02030847
Prophylaxis					
Prophylactic tocilizumab given on day 2.	Adult DLBCL treated with axi-cel.	Prophy toci: grade ≥3 CRS, 3%. Grade ≥3 ICANS, 41%. One case of cerebral edema.	No prophy toci (ZUMA-1 cohorts 1-2)[26]: grade ≥3 CRS, 13%. Grade ≥3 ICANS, 28%.	Peak IL-6 levels were higher in the prophy toci group, possibly because IL-6R antagonists increase free IL-6.	Locke et al (ZUMA-1 cohort 3)[27] NCT02348216
Prophylactic dexamethasone 10 mg on days 0, 1, and 2.	Adult DLBCL treated with axi-cel.	Prophy dex: grade ≥3 CRS, 0%. Grade ≥3 ICANS, 13%.	No prophy dex (ZUMA-1 cohorts 1-2): grade ≥3 CRS, 13%. Grade ≥3 ICANS, 28%.	Lower baseline tumor burden than ZUMA-1 cohorts 1-2.	Oluwole et al (ZUMA-1 cohort 6)[28] NCT02348216
Prophylactic anakinra given on days 0-7.	Adult DLBCL treated with axi-cel.	Prophy anakinra: grade ≥2 CRS, 40%. Grade ≥3 ICANS, 20%	No prophy anakinra, tumor burden–matched retrospective cohort: grade ≥2 CRS, 70%. Grade ≥3 ICANS, 50%.	Early follow-up suggests efficacy preserved.	Strati et al[29] NCT04432506
Prophylactic anakinra. Started at first fever, or day 2 if no fever. Continued for a minimum of 10 days.	Adult DLBCL and MCL treated with axi-cel, tisa-cel, and brexu-cel.	Prophy anakinra: grade ≥3 CRS, 6%. Grade ≥3 ICANS, 6%.	No specific comparison cohort.	Early follow-up suggests efficacy preserved.	Park et al[30] NCT04148430
Concurrent BTK inhibition					
Ibrutinib + CAR T cells.	Adult CLL treated with CD19 CAR T cells.	Concurrent ibrutinib: grade ≥3 CRS, 0%. Grade ≥3 ICANS, 26%.	No concurrent ibrutinib, earlier cohort of same trial: grade ≥3 CRS, 11%. Grade ≥3 ICANS, NA.	Better CAR T-cell expansion with concurrent ibrutinib, no difference in efficacy.	Gauthier et al[32] NCT01865617
Concurrent JAK inhibition					
Itacitinib + CAR T cells.	Adult DLBCL or MCL (90% of patients) treated with axi-cel, tisa-cel, or brexu-cel.	Concurrent itacitinib: grade ≥3 CRS 2%. Grade ≥3 ICANS, 13%.	No specific comparison cohort.	Randomized phase 2 (itacitinib vs placebo) underway, treating DLBCL/FL with axi-cel.	Pratta et al[33] NCT04071366

Jain, Michael D et al. "How I treat refractory CRS and ICANS after CAR T-cell therapy." *Blood* vol. 141,20 (2023)

Complicações Imunológicas Precoces

Hematotoxicidade

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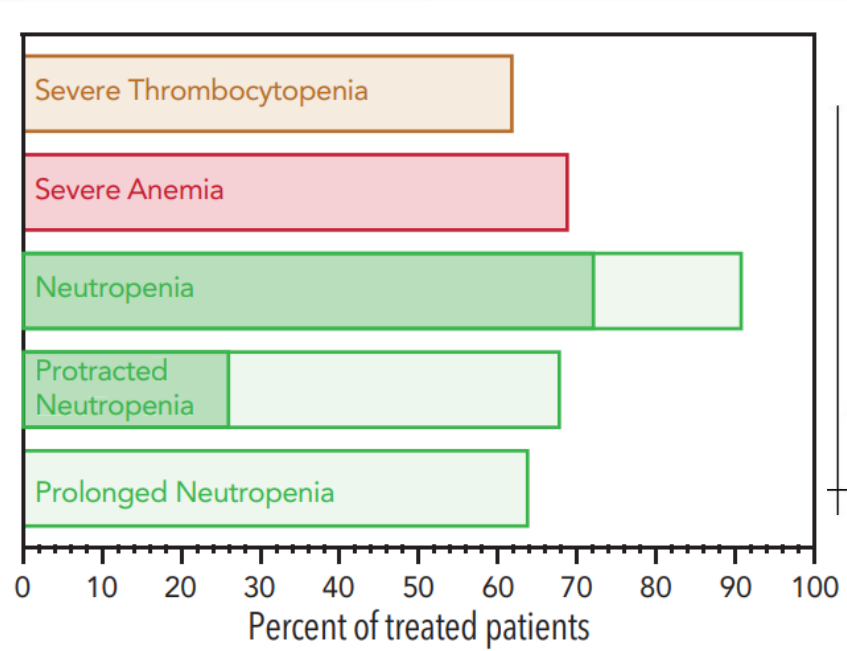
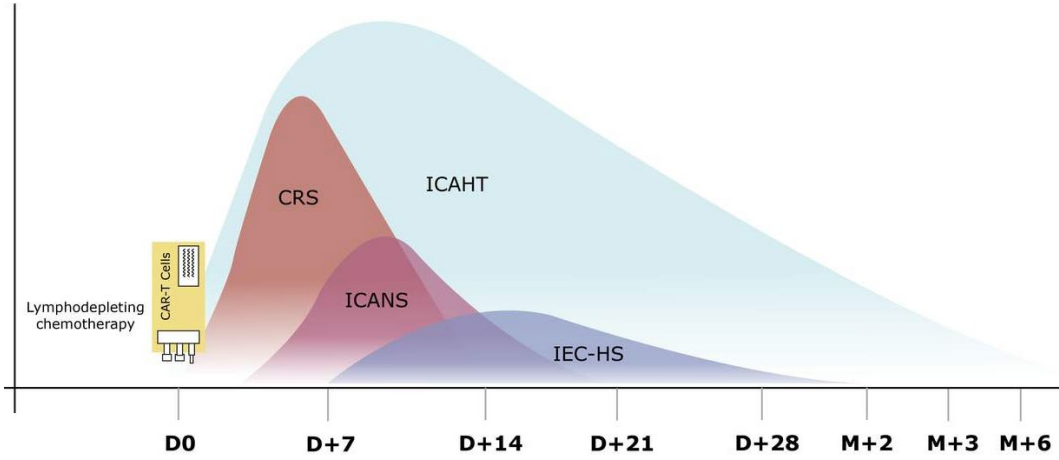
Innovative Medicine

Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

- Prevalência e Factores de Risco





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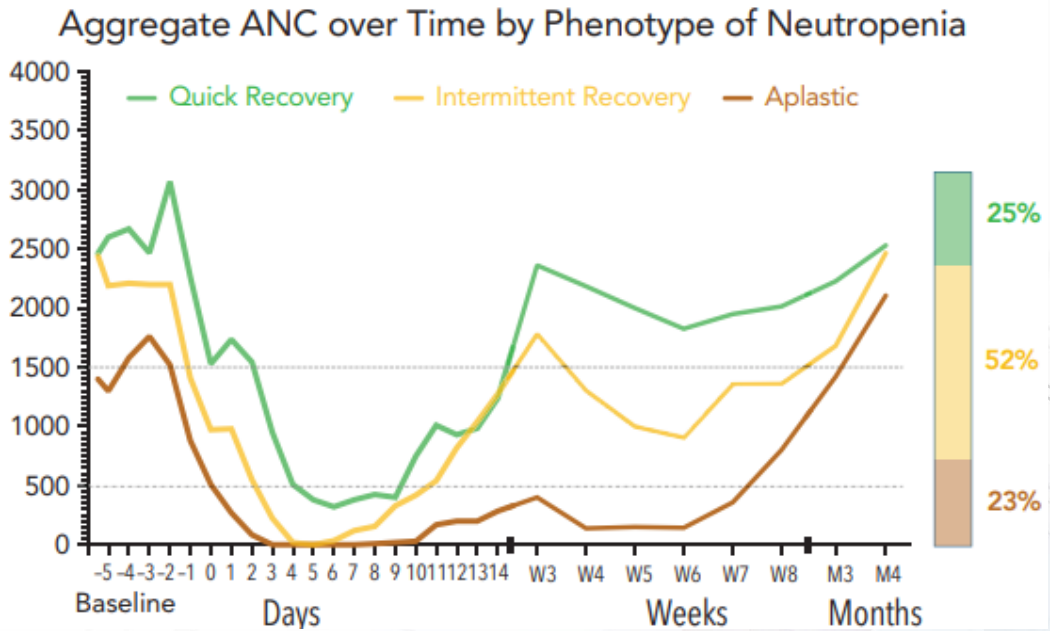
Rejeski, Kai et al. "CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma." *Blood* vol. 138,24 (2021)

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ Prevalência e Factores de Risco

3 Fenótipos distintos:

- Recuperação Rápida
  - Reparação sustentada sem nova descida < 1000/uL
- Recuperação Intermitente
  - Recuperação seguida de nova descida < 1000/uL após D+21
- Aplástico
  - Neutrofilos <500/uL durante ≥14 dias



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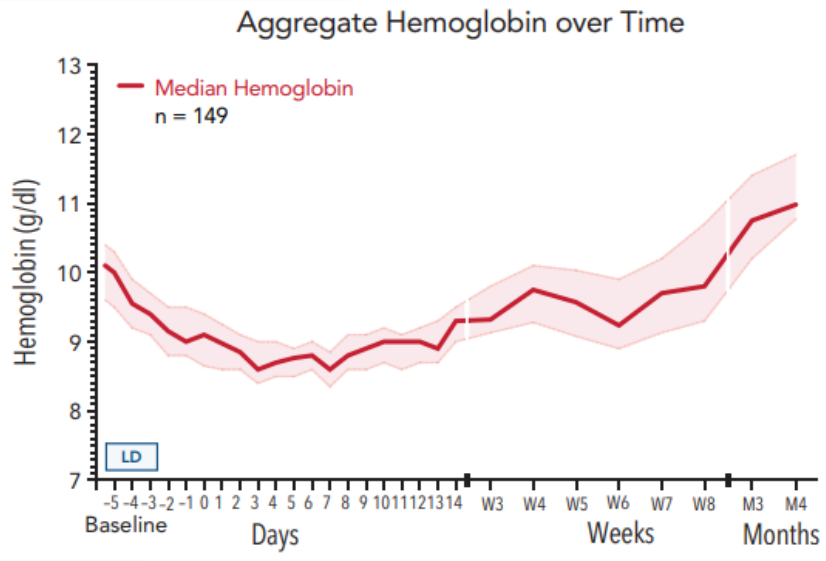
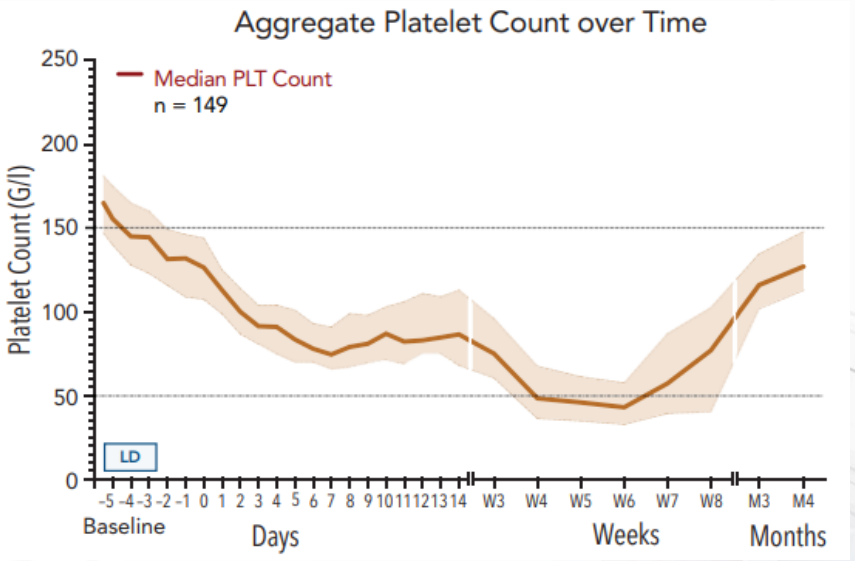
Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

- Prevalência e Factores de Risco





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Rejeski, Kai et al. "CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma." *Blood* vol. 138,24 (2021)

Hematotoxicidade (ICAHT)

➢ Prevalência e Factores de Risco

- Tipo de CAR-T cell
  - Coestimulador CD28 > 41BB
- Tipo de neoplasia e carga tumoral
- Reserva medular
  - Infiltração
  - Nº linhas prévias
  - Citopénias prévias
  - CHIP (?)
- Estado Inflamatório
  - Basal (PCR, Ferritina)
  - CRS, IEC-HS, Infeções

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ *Scores* de Risco

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%

	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%

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Rejeski, Kai et al. "CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma." *Blood* vol. 138,24 (2021)

Complicações da terapia CAR-T
Hematotoxicidade (ICAHT)

➢ *Scores* de Risco

Transplantation and Cellular Therapy 30 (2024) 404–414

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Full Length Article
Cellular Therapy

Clinical Impact of Cytokine Release Syndrome on Prolonged Hematotoxicity after Chimeric Antigen Receptor T Cell Therapy: KyoTox A-Score, a Novel Prediction Model

Naokazu Nakamura[1], Tomoyasu Jo[1,2], Yasuyuki Arai[1,2,*], Toshio Kitawaki[1], Momoko Nishikori[1,3], Chisaki Mizumoto[1], Junya Kanda[1], Kouhei Yamashita[1], Miki Nagao[2], Akifumi Takaori-Kondo[1,2]

Variável	0 Pontos	1 Ponto	2 Pontos
m-CRS	Grau ≤ 1a	–	Grau ≥ 1b
Valor max PCR	< 10 mg/mL	≥ 10 mg/dL	–
Duração elevação PCR	< 10 d	≥ 10 d	–
↓ Fosfato	Não	Sim	–

KyoTox A-Score Baixo (0-1 Pontos)

KyoTox A-Score Alto (2-5 Pontos)

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Complicações da terapia CAR-T

Hematotoxicidade (ICAHT)

➢ Graduação

	Grau 1	Grau 2	Grau 3	Grau 4
ICAHT Precoce (D0–30)				
Neut ≤500/µL	< 7 dias	7 – 13 dias	≥ 14 dias	Nunca >500/µL
Neut ≤100/µL	—	—	≥ 7 dias	≥ 14 dias
ICAHT Tardio (após D30)				
Neut	≤ 1500/µL	≤ 1000/µL	≤ 500/µL	≤ 100/µL

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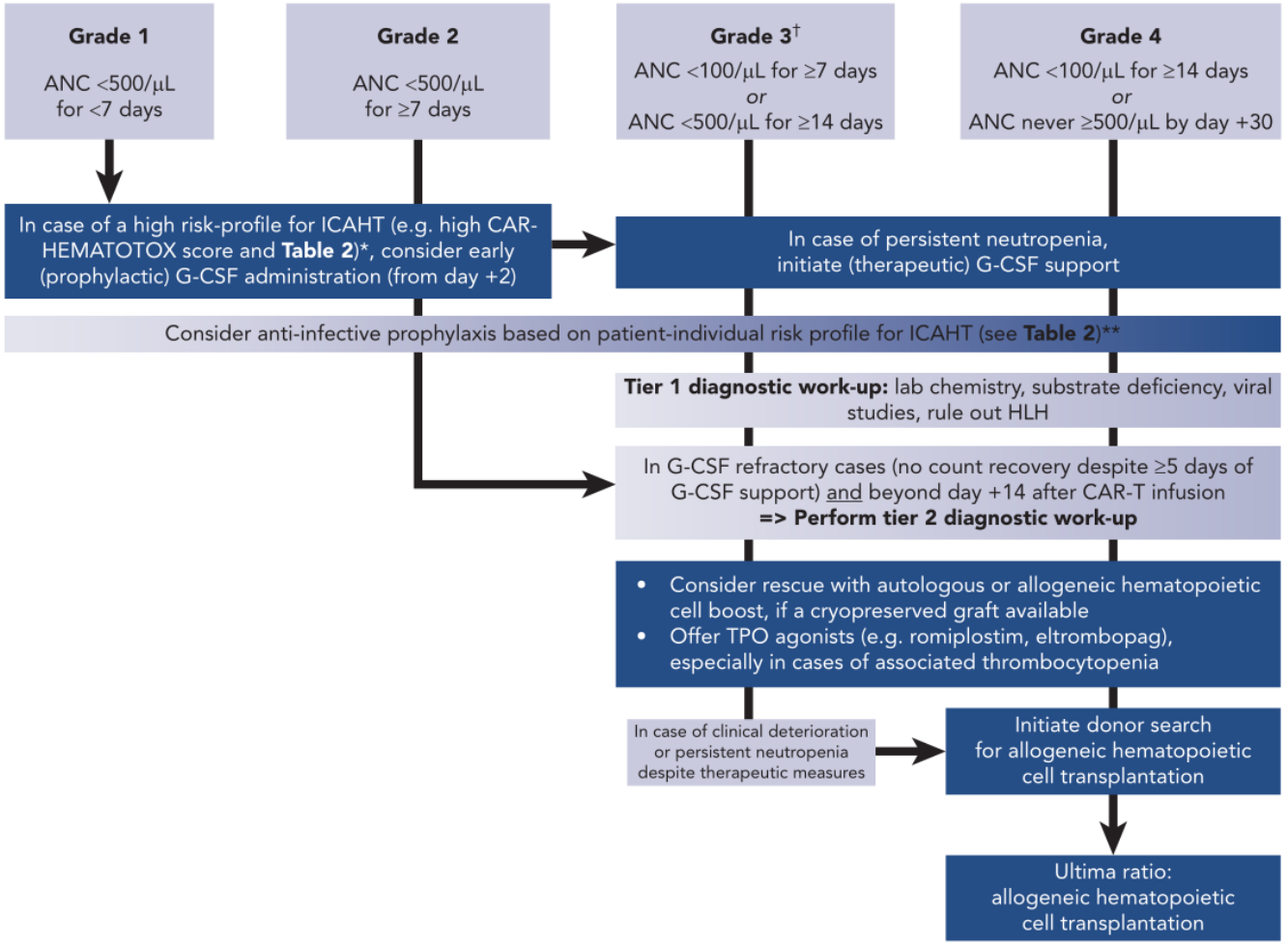
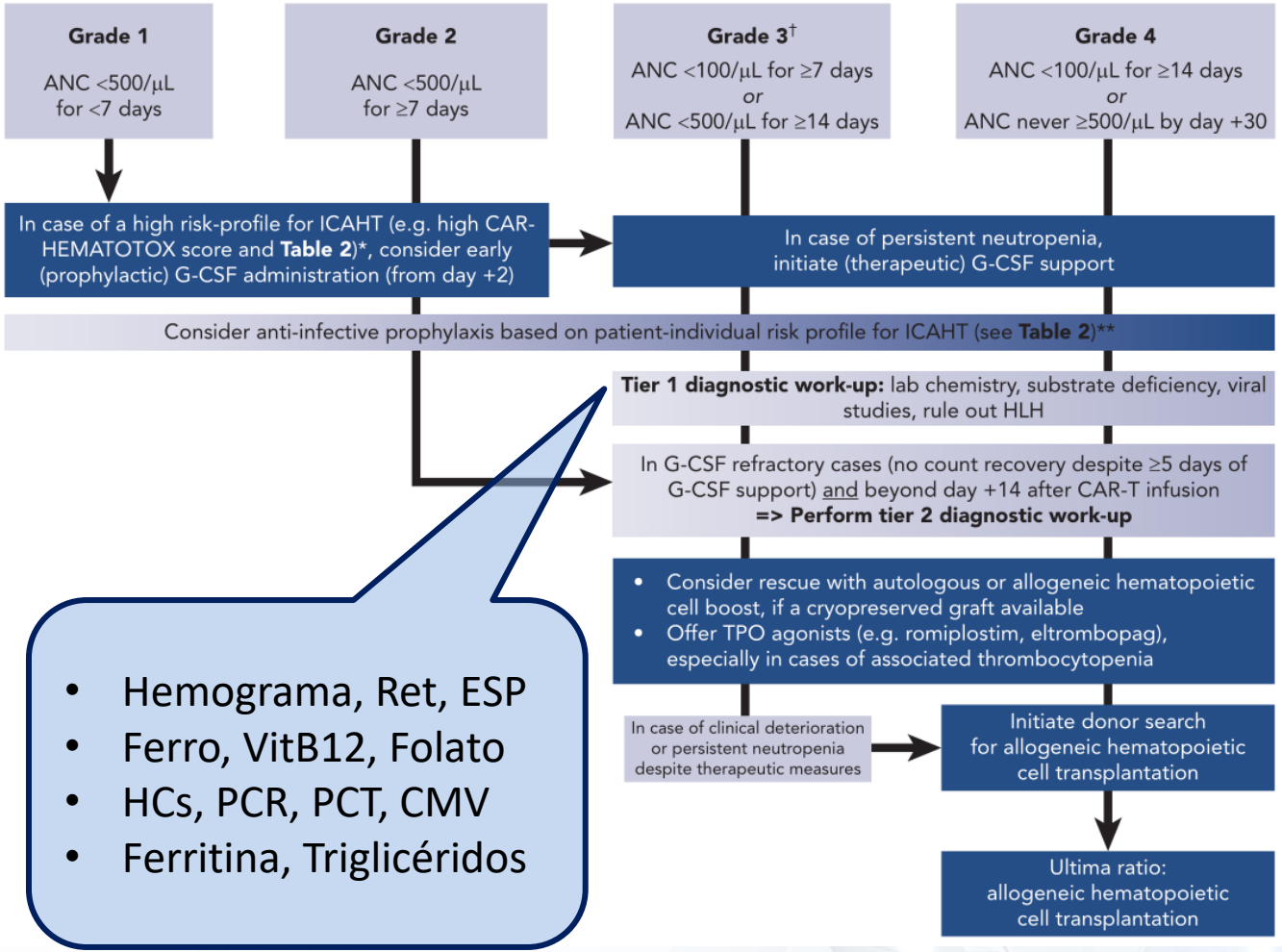
Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



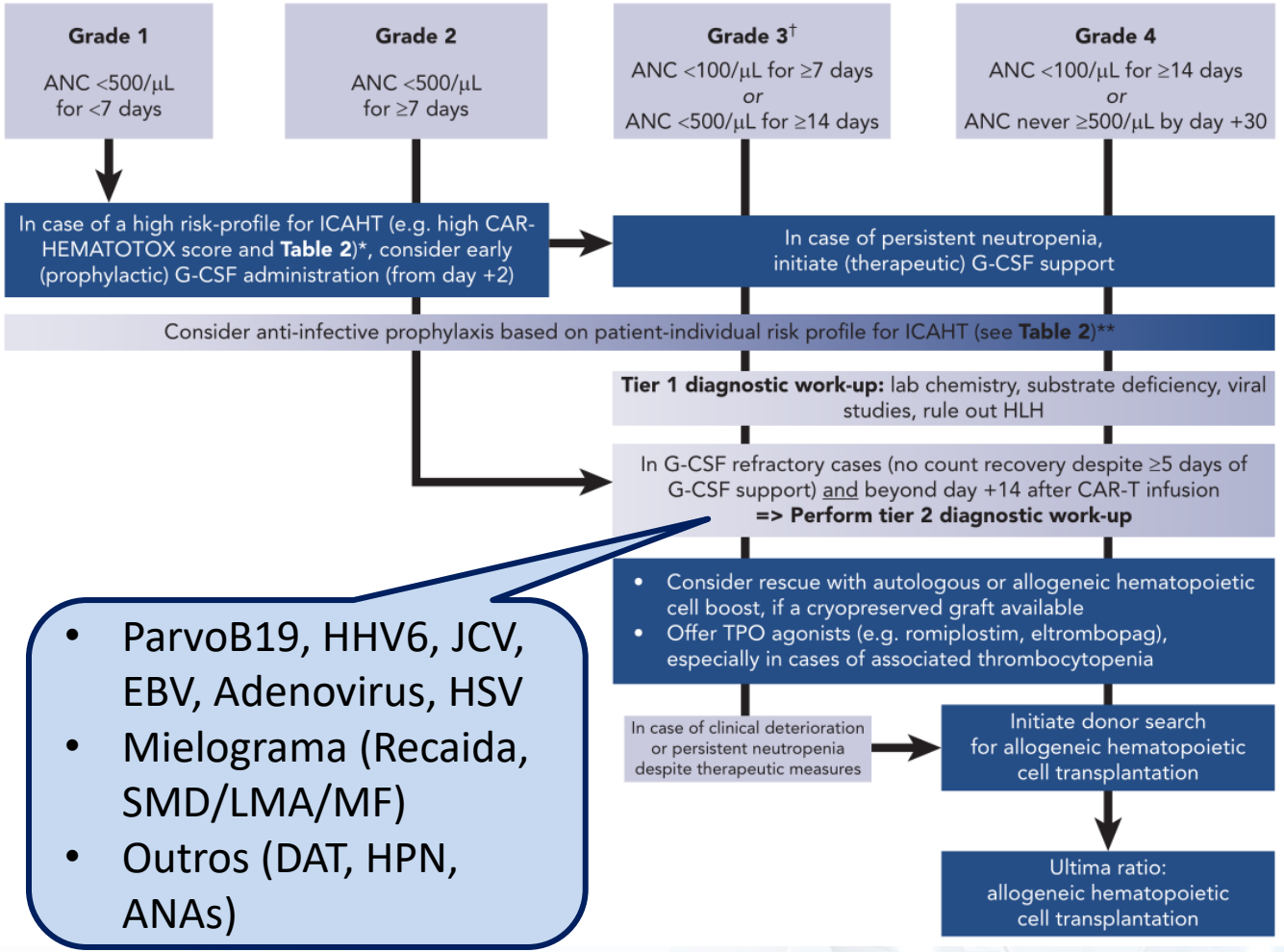
Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



Complicações da terapia CAR-T
ICATH

- Abordagem Terapêutica



- ParvoB19, HHV6, JCV, EBV, Adenovirus, HSV
- Mielograma (Recaida, SMD/LMA/MF)
- Outros (DAT, HPN, ANAs)

Toxicidades imunológicas e risco de infeção

Francys Llanos

Índice

Não conflitos de interesses

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OS DOENTES QUE RECEBEM INFUSÃO DE CÉLULAS CAR-T TÊM RISCO DE INFEÇÃO?

Infection. 2020 Sep 26;49(2):215–231. doi: 10.1007/s15010-020-01521-5

Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper

Ibai Los-Arcos [1,2], Gloria Iacoboni [3,4], Manuela Aguilar-Guisado [5], Laia Alsina-Manrique [6], Cristina Díaz de Heredia [7], Claudia Fortuny-Guasch [8], Irene García-Cadenas [9], Carolina García-Vidal [10], Marta González-Vicent [11], Rafael Hernani [12], Mi Kwon [13], Marina Machado [14], Xavier Martínez-Gómez [15], Valentín Ortiz Maldonado [16,17], Carolina Pinto Pla [18], José Luis Piñana [19], Virginia Pomar [20], Juan Luis Reguera-Ortega [21], Miguel Salavert [22], Pere Soler-Palacín [23], Lourdes Vázquez-López [24], Pere Barba [3,4,✉], Isabel Ruiz-Camps [1,2]

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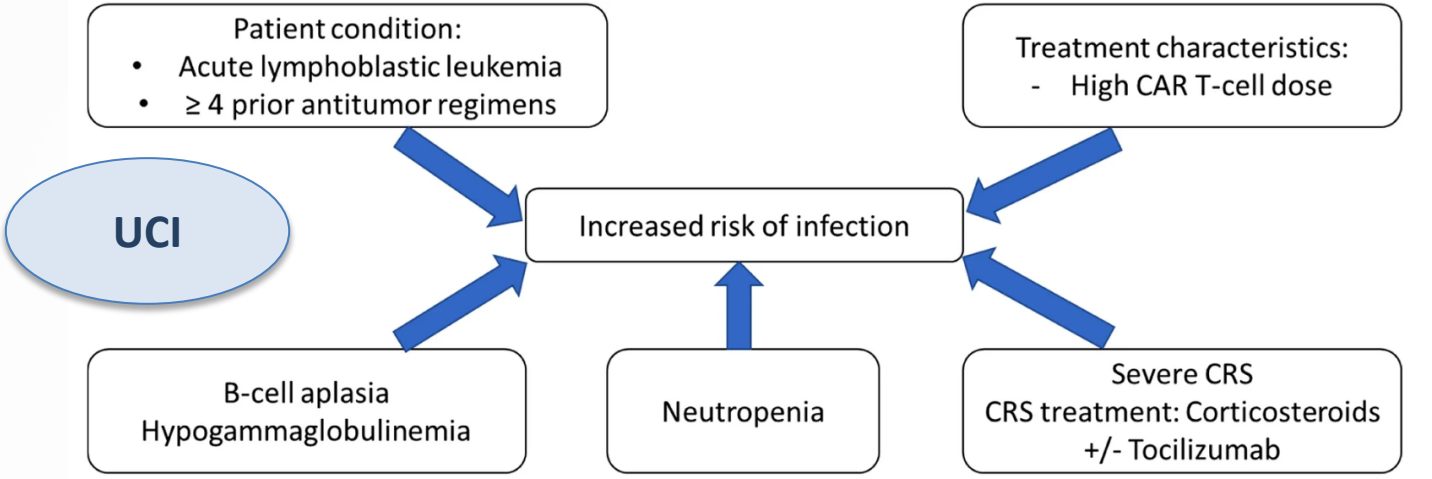
PMCID: PMC7518951 PMID: 32979154



Risk factors for infection in patients receiving CAR T cells

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QUAIS SÃO OS FATORES DE RISCO ASSOCIADOS A INFEÇÕES GRAVES?

IMMUNOBIOLOGY AND IMMUNOTHERAPY | JANUARY 4, 2018

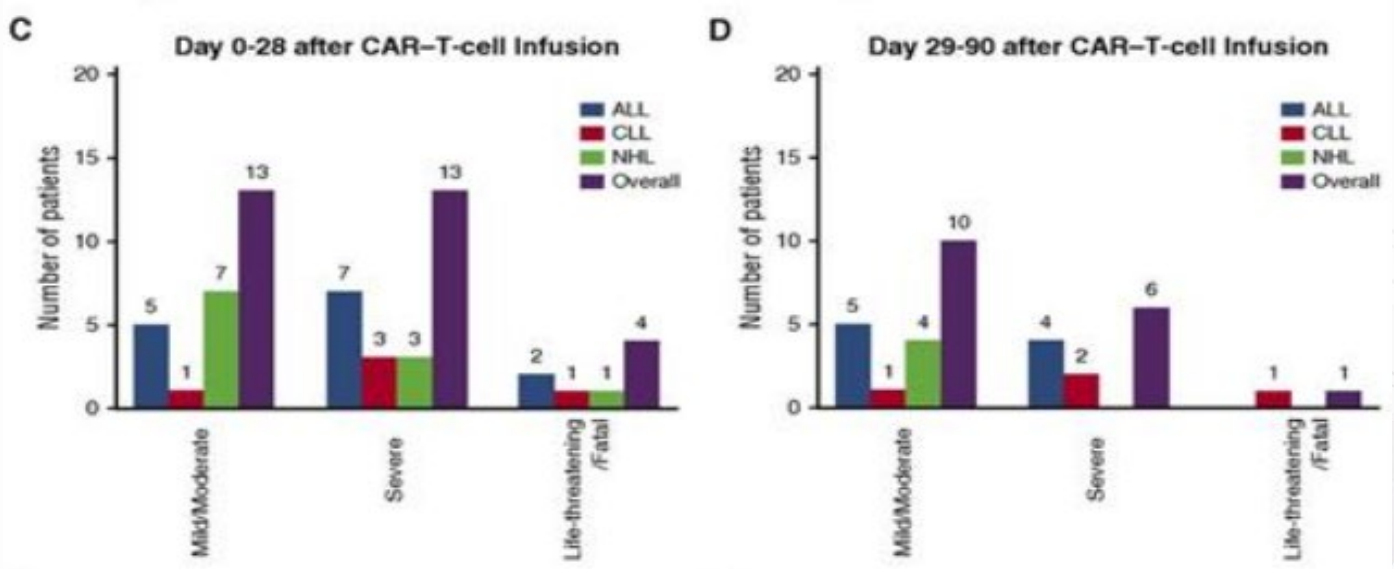
Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy

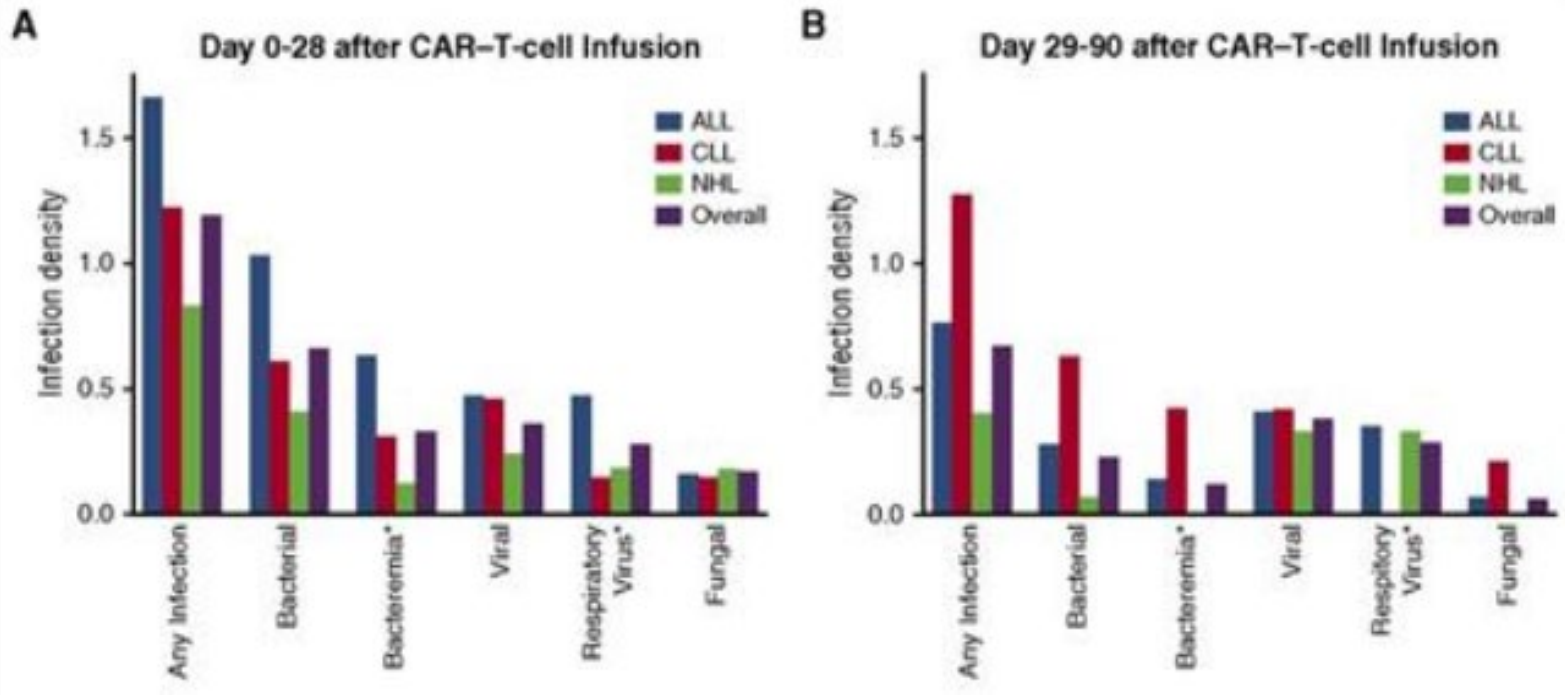
Clinical Trials & Observations

Joshua A. Hill, Daniel Li, Kevin A. Hay, Margaret L. Green, Sindhu Cherian, Xueyan Chen, Stanley R. Riddell, David G. Maloney, Michael Boeckh, Cameron J. Turtle

Check for updates

Blood (2018) 131 (1): 121–130.





Hill J et al. Infections of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood (2018) 131 (1): 121-130

Johnson&Johnson
Innovative Medicine

Blood Cancer J. 2020 Aug 5;10(8):79. doi: 10.1038/s41408-020-00346-7

Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma

Kitsada Wudhikarn [1,2,#], M Lia Palomba [3,4,#], Martina Pennisi [1,5], Marta Garcia-Recio [1], Jessica R Flynn [6], Sean M Devlin [6], Aishat Afuye [1], Mari Lynne Silverberg [1], Molly A Maloy [1], Gunjan L Shah [1,4], Michael Scordo [1,4], Parastoo B Dahi [1,4], Craig S Sauter [1,4], Connie L Batlevi [3,4], Bianca D Santomasso [4,7], Elena Mead [4,8], Susan K Seo [4,9], Miguel-Angel Perales [1,4,✉]

Variáveis	HR (95% IC)	p-Valeu	Risco
Uso do corticoide sistémico durante o CAR-T	2.22 (1.05-4.67)	0.03	Fator preditor de risco para complicações infeciosas
ECOG-PS (≥2 vs. 1).	2.84 (1.01-8.06)	0.05	Associadas a infeções bacterianas graves
Infeções antes do CAR-T	3.98 (1.30-12.20)	0.01	
IgG <400mg/dL antes do CAR-T	5.73 (2.29-14.30)	<0.001	Maior risco de infeções virais

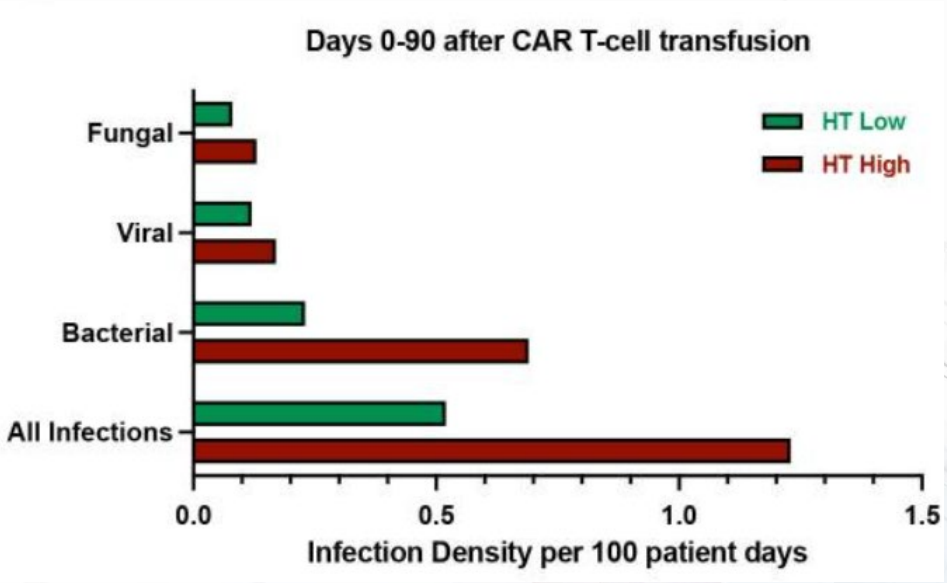
J Immunother Cancer. 2022 May 17;10(5):e004475. doi: 10.1136/jitc-2021-004475

The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T in R/R LBCL

Kai Rejeski [1,2,3], Ariel Perez [4,5], Gloria Iacoboni [6], Olaf Penack [7,8], Veit Bücklein [1,2], Liv Jentzsch [9], Dimitrios Mougiakakos [10], Grace Johnson [11], Brian Arciola [11], Cecilia Carpio [6], Viktoria Blumenberg [1,2], Eva Hoster [12], Lars Bullinger [7,8], Frederick L Locke [4], Michael von Bergwelt-Baildon [1,3], Andreas Mackensen [10], Wolfgang Bethge [9], Pere Barba [6], Michael D Jain [4], Marion Subklewe [1,2,3]

- Calcular antes da LD (dia -5).
- Compreende 5 marcadores de hemato-toxicidade (P; N; Hb; PCR; Ft).
- Discrimina entre risco elevado (pontuação CAR-HEMATOTOX ≥2) e baixo (0-1).

https://www.german-lymphoma-alliance.de/Scores.html



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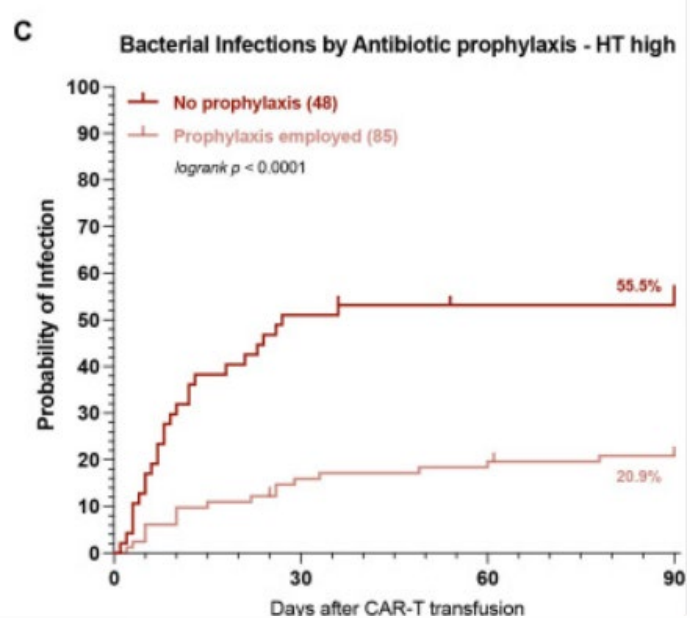

FLUOROQUINOLONAS

Variáveis	HR (95% IC)	p-Valeu	Risco
CAR-HEMATOTOX (≥2)	6.14 (2.93-12.87)	<0.0001	Infeções de grau ≥3
N grave ≥14 dias (<500/µL D0-D+60)	3.13 (1.74-5.62)	<0.001	

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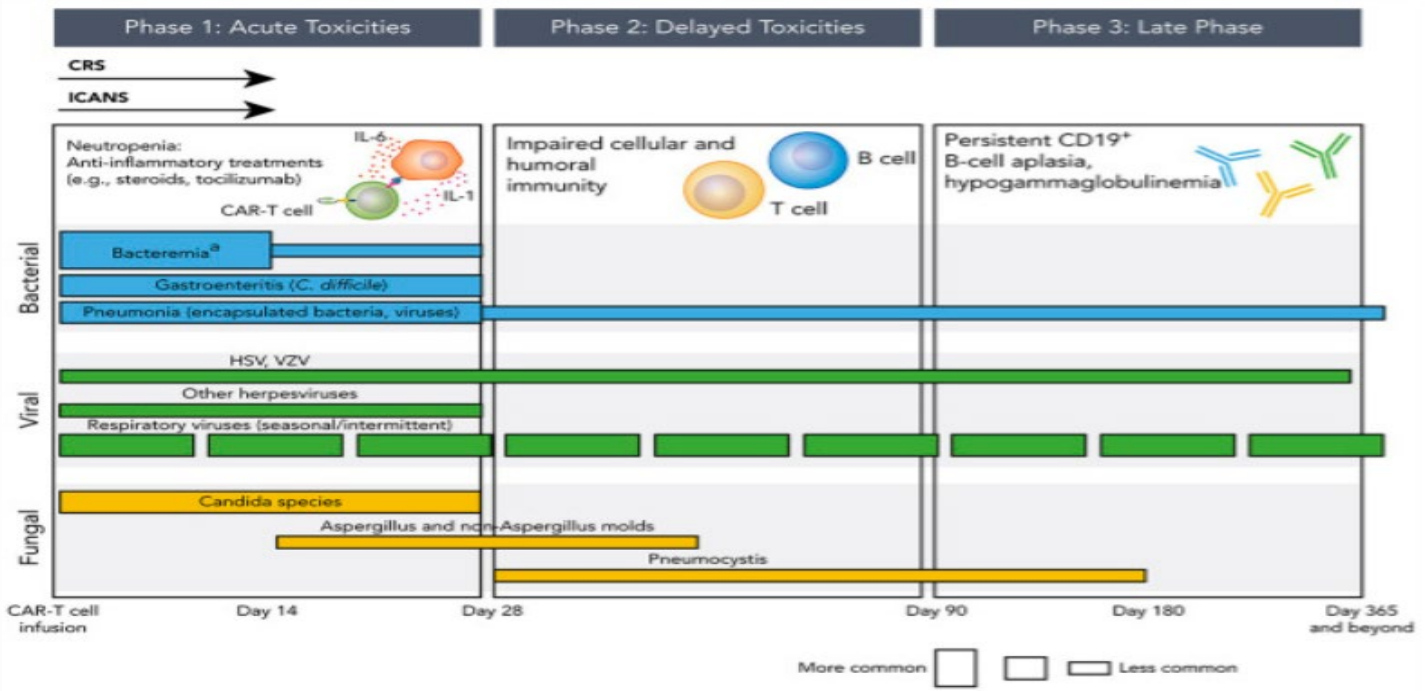
Rejeski K et al. The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CD19 CAR-T in R/R LBCL. JIC 2022 May 17; 10(5):e004475

QUAIS SÃO ESSAS INFEÇÕES?
EPIDEMIOLOGIA DAS INFEÇÕES

Review > Blood. 2020 Aug 20;136(8):925-935. doi: 10.1182/blood.2019004000.

How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies

Joshua A Hill [1 2 3 4], Susan K Seo [5 6]



TRANSPLANT INFECTIOUS DISEASE

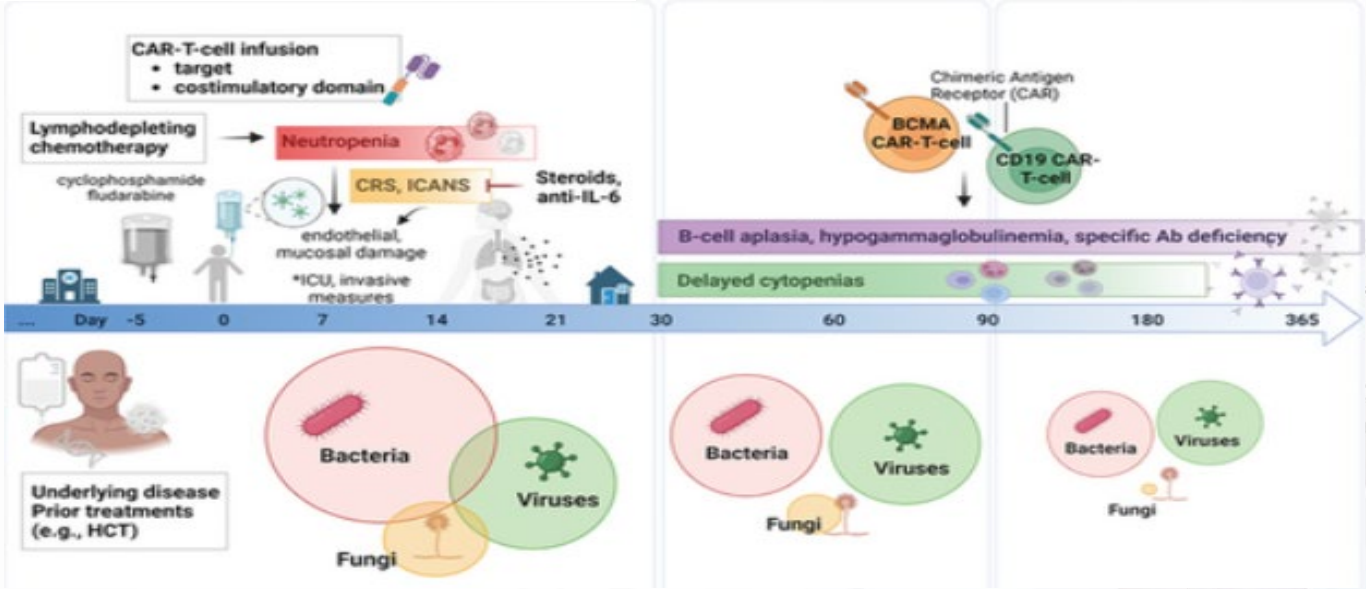
InternNet CLUB
FÓRUM 2025 • 9ª EDIÇÃO

REVIEW ARTICLE | Open Access

Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies

Eleftheria Kampouri, Jessica S. Little, Kai Rejeski, Oriol Manuel, Sarah P. Hammond, Joshua A. Hill

First published: 03 October 2023 | https://doi.org/10.1111/tid.14157 | Citations: 3



Infection risk and epidemiology during different time intervals after chimeric antigen receptor (CAR)-T-cell therapy

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Infeções Precoces

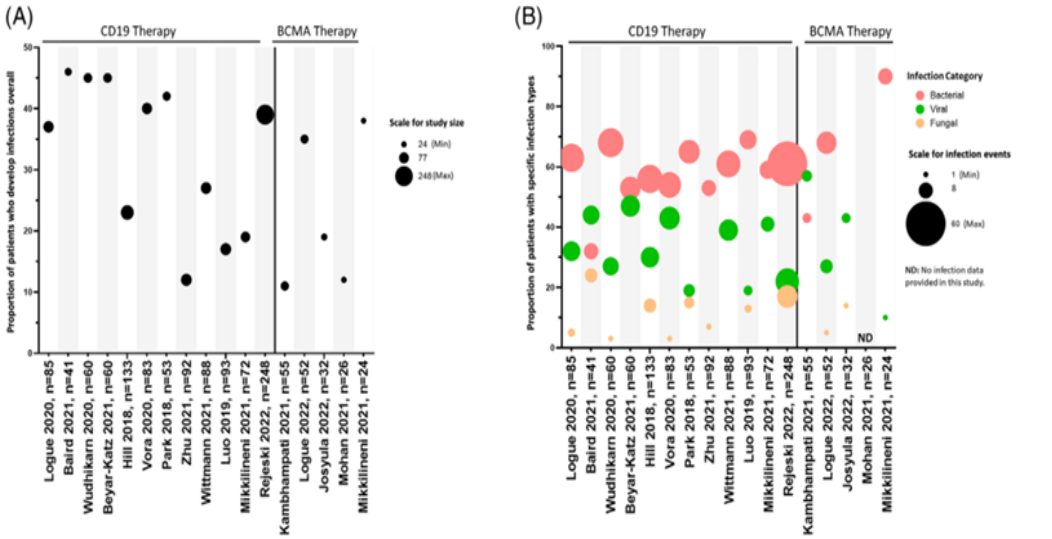
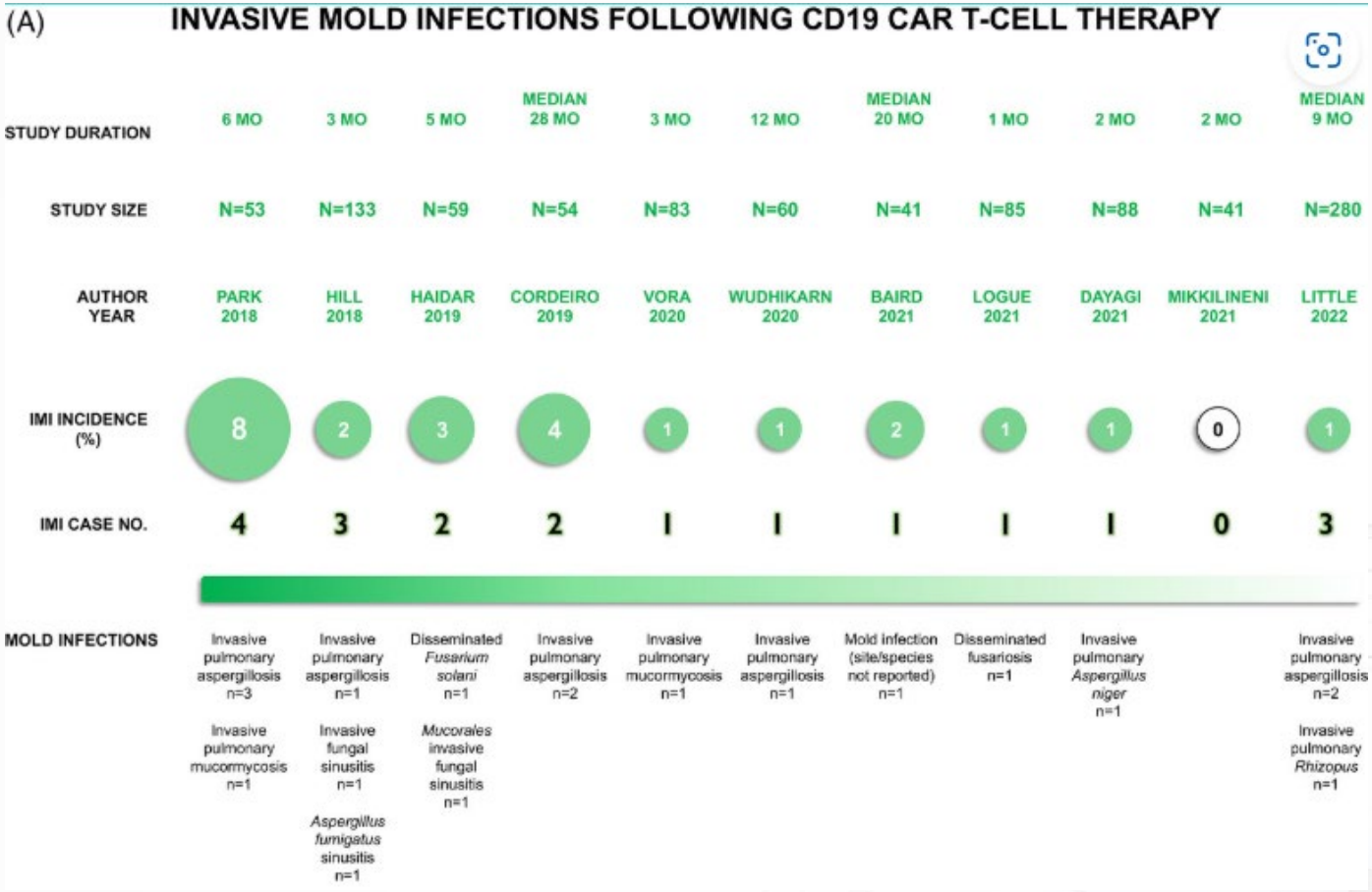


FIGURE 2 Early infections after CD19 and B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T-cell therapy (within 30 days).

- Incidência ~12-46% no 1ºM.
- As infeções bacterianas predominam durante o 1ºM, (32 a 68% de todos os eventos).
- As infeções virais representam 19 a 47% de todas as infeções, incluem vírus respiratórios.

Johnson&Johnson Innovative Medicine

Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023



As infeções fúngicas são menos comuns. (3 a 14%)

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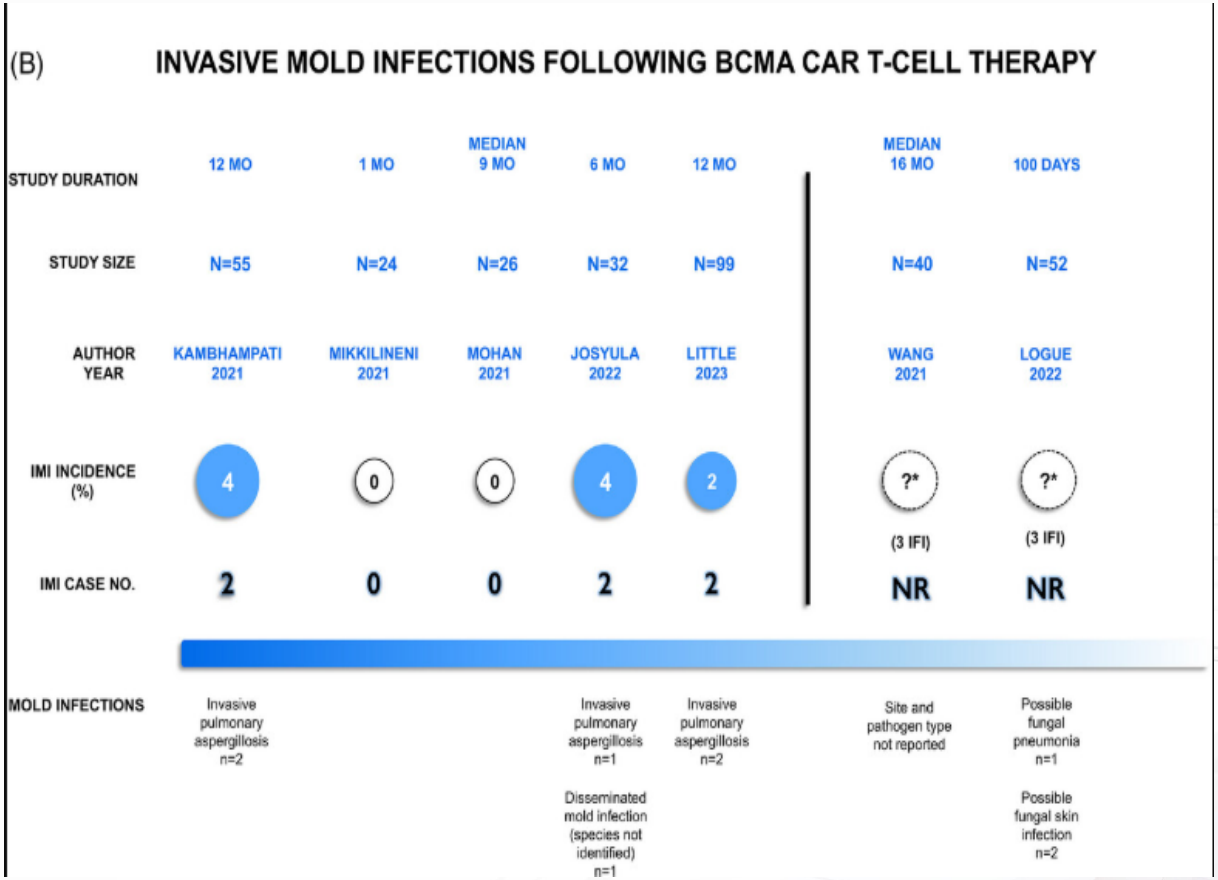
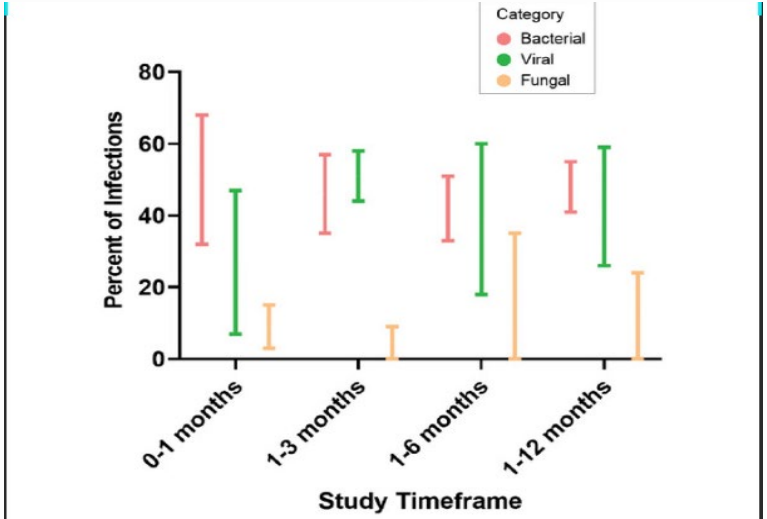
Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023



Johnson&Johnson Innovative Medicine

Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023

Infeções Tardias



Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35-38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

Relative frequency of infection types (bacterial, viral and fungal) as percentage of all infections after CD19 CAR-T-cell therapy during different time intervals

Johnson&Johnson Innovative Medicine

Kampouri E et al. Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies. TID. 03 october 2023

Review > Nat Rev Clin Oncol. 2024 Jul;21(7):501-521. doi: 10.1038/s41571-024-00903-0. Epub 2024 May 20.

Current understanding and management of CAR T cell–associated toxicities

Jennifer N Brudno [1], James N Kochenderfer [2]

- Infeções grau ≥3 (~5-32%).
- A morte relacionada com infeções após de CAR-T (~1-12% dos doentes em coortes com follow-up de 10-16M)
- Os fatores de risco pré-CAR-T para infeção incluem: o tipo de doença (LLA-B > LNH), > Nº LT, alo-TPH, QT ponte, CAR-HEMATOTOX ≥2
- N (<500células/µl x≥14D) e corticoides (DMX 10mg/dia x≥9D entre D0-D+21), são fatores de risco para infeção.

Table 1 | Rates of major CAR T cell-related toxicities for approved CAR T cell products

Product and indication	Grade 3–5 CRS (%)[a]	Vasopressor requirement (%)	Hypoxia and/or supplemental oxygen (%)	Grade 3–5 neurological toxicity (%)[b]	Ongoing B cell aplasia at 1 year in evaluable responders (%)[c]	Prolonged grade 3–4 cytopenias (%)[d]	Grade 3–5 infections (%)	Treatment-related mortality (%)	Refs.
CD19-directed CAR T cell products for large B cell lymphoma									
Axi-cel	6.5–16	6–17	22–31	21–35	47–50	29–38	16–28	1.9–5.7	4,23,42,88, 89,91,121
Tisa-cel	4.5–17[m]	1.9–3.6[l]	8.4–13.5	5.1–12[g]	NR	32	20	0–1.3	2,124,172
Liso-cel	1.1–2.2	0–2.6	10	4.3–10	73	37–43	12–15	2.2–2.6	6,173
CD19-directed CAR T cell products for follicular lymphoma									
Axi-cel	6.5	4.7[h]	22	15	52[h]	33	15	0.8	5
Tisa-cel	0	3.1	9.3	3.1	NR	Reported by individual lineages: neutropenia 15.5; thrombocytopenia 16.5; anaemia 3.1	5.2	0	3
CD19-directed CAR T cell products for mantle cell lymphoma									
Brexu-cel	3.0–15[e]	16	34	31–36[i]	55	26 at >90 days	32	2.9–15	8,90
CD19-directed CAR T cell products for B cell acute lymphoblastic leukaemia									
Tisa-cel (children and young adults)	16–47[j]	12–25[f]	17–44	9.0–13[g]	71	32	24	1.3	1,124,174
Brexu-cel (adults aged ≥18 years)	24	40	29	25	50 at 15 months	36	25	3.6	9
CD19-directed CAR T-cell products for chronic lymphocytic leukaemia									
Liso-cel	8.6	NR	14	19	74	54	17	0.73	7,175
BCMA-directed CAR T cell products for multiple myeloma									
Ide-cel	3.1–5.5[n]	NR	NR	3.1–5.7[l]	NA	Neutropenia 41–60; thrombocytopenia 48–59	23	1.9–3.1	10,24
Cilta-cel	5.2[k]	4.1	6.2	10.3[i]	NA	Neutropenia 30; thrombocytopenia 41	23	6.2	11,81

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COMO DIFERENÇAR A SÍNDROME DE LIBERTAÇÃO DE CITOCINAS DE UMA INFEÇÃO?

Open Forum Infect Dis. 2024 Jul 11;11(7):ofae398. doi: 10.1093/ofid/ofae398

Chimeric Antigen Receptor T-Cell Postinfusion Fever: Infection Profile, Clinical Parameters, and Biomarkers Trends to Assist Antibiotic Stewardship

Olivier Peyrony [1,2,#,✉], Nicole Garcia-Pouton [3,#], Mariana Chumbita [4,#], Christian Teijon-Lumbreras [5], Tommaso Francesco Aiello [6], Patricia Monzó-Gallo [7], Antonio Gallardo-Pizarro [8], Valentín Ortiz-Maldonado [9], Núria Martinez-Cibrian [10], Julio Delgado [11], Carlos Fernandez de Larrea [12], Josep Mensa [13], Pedro Puerta-Alcalde [14], Alex Soriano [15,16], Carolina Garcia-Vidal [17,✉,3]

Antibiotic	No. (%)
No.	87
Meropenem	55 (63.2)
Piperacillin-tazobactam	24 (27.6)
Teicoplanin	20 (23.0)
Levofloxacin	20 (23.0)
Ertapenem	5 (5.7)
Amikacin	5 (5.7)
Vancomycin	4 (4.6)
Others	12 (13.8)

Documented Infections in Patients With Initial Fever Post–Chimeric Antigen Receptor T-Cell Infusion

Patient	Bacteria	Virus	Fungi
1	*Staphylococcus epidermidis* (BC and catheter)	...	...
2	...	Coronavirus (BAL)	...
3	...	SARS-CoV-2 (NPS)	...
4	...	SARS-CoV-2 (NPS)	*Candida parapsilosis* (BC)
5	...	RSV (NPS)	...
6	*Enterococcus faecium* (BC)	...	...
7	*Enterococcus faecalis* (BC)	...	...
8	*Staphylococcus haemolyticus* (BC)	...	...
9	...	SARS-CoV-2 and other coronavirus (NSP)	...

No início da febre, não houve diferenças dos parâmetros clínicos e biomarcadores entre doentes sem infeção e com infeção bacteriana documentada, exceto para o score NEWS, que foi maior em doentes sem infeção (HR 5 [4–6] vs HR 3 [3–3]; p= 0,03)

- **Estudo retrospetivo, observacional – HCB**
- **152 doentes tratados com CAR-T**
- **87 (57,2%) febre – 30D após infusão**
- **Tempo médio (infusão e febre): 3D (2-5)**
- **82 (94.3%) AB amplo espectro**
- **9 (10,3) documentada infeção**
- **4 (4.6%) infeções bacterianas**

Johnson&Johnson
Innovative Medicine

Puerta P, et al. Paquete de medidas para reducir el uso de antibióticos y sus complicaciones en pacientes que reciben terapia CAR-T y presentan fiebre. FIS 2022

CAR-T cell infusion

Fever

- □ No specific signs or symptoms of infection
- □ No changes in NEWS score
- □ Negative blood cultures (at least 48h)

ANTIBIOTIC DISCONTINUATION OR DE-ESCALATION REGARDLESS OF FEVER

Johnson&Johnson
Innovative Medicine

Article | Published: 19 February 2021

CRS-related coagulopathy in BCMA targeted CAR-T therapy: a retrospective analysis in a phase I/II clinical trial

Mi Shao, Qin Yu, Xinyi Teng, Xin Guo, Guoqing Wei, Huijun Xu, Jiazhen Cui, A. H. Chang, Yongxian Hu & He Huang

Bone Marrow Transplantation **56**, 1642–1650 (2021) | Cite this article

InternNet CLUB
FÓRUM 2025 • 9ª EDIÇÃO

- Os parâmetros de coagulação e os níveis de algumas citocinas (IL-6, IL-10 e interferon [IFN]-γ) correlacionaram-se positivamente com a gravidade da CRS.
- Doentes com CRS grave apresentam níveis séricos elevados de angiopoietina 2 (ANGPT2) e fator de Von Willebrand (FVW)

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COMO PREVENIR AS INFEÇÕES?

Table 5 (continued) | Prevention, monitoring, evaluation and treatment of CAR T cell-related haematological and immunological toxicities

Pretreatment assessment	Preventive measures	Post-treatment monitoring	Diagnostic evaluation if toxicity occurs	Supportive care measures	Pharmacological and/or immunological management[a]
Immunosuppression and infections, except COVID-19 (refs. 22,26,47,48,129,130,179)					
Pre-leukapheresis serologies for EBV, HBV, HCV, HIV, HSV, VZV and CMV; HBV PCR for viral DNA if HBV surface antigen or core antibody-positive, and HCV PCR for viral RNA if HCV antibody-positive Consider PCR testing for EBV, CMV and HBV regardless of serology results Treatment of individuals with HIV infection can be made on a case-by-case basis[b]	Delay lymphodepletion and/or CAR T cell infusion if patient is febrile and has evidence of infection and give appropriate antimicrobial treatment; resume CAR T cell therapy when patient is afebrile for at least 48 h and clinical evidence suggests that the infection is controlled and symptoms have improved Delay treatment in patients with detectable HBV or HCV DNA/RNA or HBV surface antigen positivity until infection is treated Entecavir or tenofovir prophylaxis in patients with HBV core antibodies, for at least 6 months to 1 year after cell infusion; consider longer in those with continued B cell aplasia All patients should receive prophylactic antimicrobials for pneumocystis and HSV and VZV infection for 6 months to 1 year after cell infusion; consider longer if blood $CD4^+$ cell counts are <200 cells/μl; re-vaccinate with killed/inactivated and live attenuated vaccines >6 months and ≥12 months after CAR T cell infusion, respectively, and when $CD4^+$ and B cell counts are >200 cells/μl. Immunosuppressive treatments, such as systemic chemotherapy, or immunoglobulin replacement therapy for hypogammaglobulinaemia should have been discontinued for ≥2 months prior to re-vaccination with killed/inactivated vaccines and for ≥8 months when using live attenuated vaccines, with the exception influenza and COVID-19 vaccines (see guidance below)	Check immunoglobulin levels monthly Check $CD4^+$ cell count and B cell count every ~3 months HBV viral DNA monitoring in core antibody-positive patients Consider weekly CMV PCR monitoring in seropositive individuals who have received >3 days of glucocorticoids, until 1 month after last dose of glucocorticoids	Rule out infectious causes of fever: blood cultures; depending on symptomatology, nasal swab for SARS-CoV-2 and other respiratory viruses, urine cultures and sputum cultures	Immunoglobulin replacement therapy for serum IgG levels <400–600 mg/dl or recurrent infections; replacement given more routinely in children; can consider cessation of replacement in adults >3 months after CD19-directed CAR T cell infusion Consider antifungal and gram-negative antibacterial prophylaxis in the following circumstances: intensive lymphodepletion regimens (for example, containing an anti-CD52 antibody), prolonged glucocorticoid use and/or prolonged neutropenia	Treat identified bacterial, fungal or influenza infections according to institutional guidelines in immunosuppressed individuals Empiric antibiotics for neutropenic fever

Johnson&Johnson
Innovative Medicine

Brudno J et al. Current understanding and management of CAR-T cell-associated toxicities. NRCO. 2024 Jul;21(7);501-521

Table 5 (continued) | Prevention, monitoring, evaluation and treatment of CAR T cell-related haematological and immunological toxicities

Pretreatment assessment	Preventive measures	Post-treatment monitoring	Diagnostic evaluation if toxicity occurs	Supportive care measures	Pharmacological and/or immunological management[a]
COVID-19 infection[136,178,180]					
PCR testing for SARS-CoV-2 2–3 days before lymphodepletion chemotherapy	Delay lymphodepletion chemotherapy for at least 14–20 days and until symptom improvement in patients with SARS-CoV-2 infection/ COVID-19 Counsel masking and social distancing during periods of high community infection rates Prior to CAR T cell infusion, vaccinate against influenza and COVID-19, if patient's vaccinations are not already up to date Care-givers should follow CDC guidelines for COVID-19 vaccination based on age and health status Re-vaccination for COVID-19 and influenza ≥90 days after CAR T cell infusion	Counsel patients and care-givers to monitor for symptoms and seek care promptly	SARS-CoV-2 PCR testing, with concurrent testing for influenza and RSV in patients with respiratory symptoms In patients with COVID-19 symptoms and negative nasal PCR testing for SARS-CoV-2, consider repeat testing and chest CT imaging ± bronchoscopy to evaluate for lower respiratory infection and other infectious causes	Consider early hospital admission of symptomatic patients for monitoring, depending on institutional resources	Nirmatrelvir and ritonavir or best available antiviral therapy for prevention of hospitalization and death in outpatients with COVID-19 infection; remdesivir or best available antiviral therapy for inpatients with COVID-19, except those with critical illness; dexamethasone for inpatients with COVID-19 requiring supplemental oxygen; anti-cytokine therapy (tocilizumab) or JAK inhibitors can be considered in those with worsening illness (infectious disease consultation recommended) High-titre convalescent plasma can be considered in outpatient or inpatient settings, with most benefit early in the course of illness, or in patients with protracted illness

Brudno J et al. Current understanding and management of CAR-T cell-associated toxicities. NRCO. 2024 Jul;21(7);501-521

TABLE 1 Guidelines and local practices for infection prevention in chimeric antigen receptor (CAR)-T-cell therapy recipients at the authors' centers and from published guidelines.

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antibacterial prophylaxis	NR	NR	NR	FQ during neutropenia[a]	Levofloxacin 500 mg/day during neutropenia[a]	NR	Risk adapted[b]; FQ during neutropenia[a]
Antifungal prophylaxis	Consider fluconazole, posaconazole,[c] or micafungin if severe or prolonged >14 days neutropenia,[a] and/or long-term or high dose (>3 days) of steroids or post-allo-HCT	Fluconazole (400 mg/day) during neutropenia[a]	Consider fluconazole or micafungin if severe neutropenia[a] >14 days, steroids >3 days, post-allo-HCT	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis	Fluconazole (200 mg/day) during neutropenia[a]	No antifungal prophylaxis
Anti-mold prophylaxis	See above	Posaconazole 300 mg/day,[c] nebulized liposomal amphotericin B or micafungin if ≥4 lines of prior treatment, pre-CAR-T-cell infusion severe neutropenia[a], higher dose of CAR-T-cells ($>2 \times 10^7$), previous IFI, tocilizumab, and/or steroids	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Posaconazole (300 mg/day[c]) if neutropenia[a] >20 days or steroids >3 days for at least 4 weeks after last dose of steroid (and after neutropenia resolution[a])	No anti-mold prophylaxis	Posaconazole (300 mg/day[c]) if post-allo-HCT or steroids or previous IFI	Risk-adapted[b] (posaconazole[c] or micafungin during neutropenia[a] or extended steroid exposure)
Anti-PjP prophylaxis	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 3×/week Start 1 week pre-infusion (pause during neutropenia), continue until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	TMP/SMX DS 2×/day on 2 consecutive days/week Start 21–28 days post-infusion, continue for at least 6 months	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week (or SS 1×/day) Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	TMP/SMX 1DS 3×/week Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3

	EBMT/EHA (Europe)	Spanish group (Spain)	SFGM-TC (France)	Fred Hutch (US)	Dana Farber (US)	CHUV Lausanne (Switzerland)	LMU Munich (Germany)
Antiviral prophylaxis	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for 1 year and until CD4 >200 cells/mm^3	Acyclovir 400–800 mg 2x/day At least 60–100 days after infusion	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for 1-year and until CD4 >200 cells/mm^3	Acyclovir 800 mg 2x/day or valacyclovir 500 mg 2x/day Start at lymphodepleting chemotherapy, continue for at least 1 year	Acyclovir 400 mg 3x/day or valacyclovir 500 mg 2x/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3	Valacyclovir 500 mg 2x/day for 6–12 months	Acyclovir 400 mg 2x/day Start at LD chemotherapy, continue for at least 6 months or until CD4 >200 cells/mm^3
CMV monitoring	As clinically indicated	NR	Consider in CMV seropositive patients at high risk Weekly monitoring	Patients treated with >3 days of steroids Weekly until 1 month after last dose of steroid	Strongly consider monitoring for patients receiving >5 doses dexamethasone	Consider in CMV seropositive patients at high risk Weekly/biweekly monitoring	NR
Preemptive threshold	–	NR		150 IU/mL (plasma)	None	None	None

Abbreviations: Allo-HCT, allogeneic hematopoietic cell transplant; CHUV, Lausanne University Hospital; CMV, cytomegalovirus; DS, double strength; EBMT, European Society for Blood and Marrow Transplantation; FQ, fluoroquinolone (levofloxacin 750 mg PO daily); IFI, invasive fungal infection; LD, lymphodepleting; LMU, Ludwig Maximilian University of Munich; NR, not recommended; PjP, *Pneumocystis jirovecii* pneumonia; SFGM-TC, Société de Greffe de Moelle et de Thérapie Cellulaire; SS, single strength; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Neutropenia defined as absolute neutrophil count <500 cell/mm^3; resolution: first of 3 days ≥500 cell/mm^3.

[b]Adapted to baseline CAR-Hematotox score or other pertinent risk factors for prolonged severe neutropenia (absolute neutrophile count <500 cell/mm^3 for ≥7 days) such as underlying bone marrow infiltration.

[c]Posaconazole 200 mg every 12 h on first day then 300 mg/day.

frontiers in Oncology

Front Oncol. 2024 Jul 3;14:1398078. doi: 10.3389/fonc.2024.1398078

Overview of infectious complications among CAR T- cell therapy recipients

Swarn Arya [1], Zainab Shahid [1,2,*]

Proposed Antimicrobial Prophylaxis for CAR-T Patients (4, 86–90).

	Agent	Alternative agent (s)	Comment
Antibacterial	Levofloxacin		Start when ANC < 500 and continue until neutrophil recovery (ANC >500 for at least 3 days)
Antifungal	Fluconazole	Micafungin	Start when ANC<500 and continue until neutrophil recovery (ANC >500 for at least 3 days)
Anti-mold	Voriconazole	Posaconazole	Consider in those at high risk for mold infection: ANC<500 for >21 days, treatment with prednisone >20mg for >2 weeks or equivalent, history of IFI, history of allogeneic HSCT; duration determined case by case
Anti-PJP	Trimethoprilm/ Sulfamethoxazole (TMP/SMX)	Inhaled pentamidine OR dapsone OR atovaquone	Start with lymphodepleting chemotherapy and continue for at least 6 months post- CAR T infusion or until CD4 count >200 cell/mm^3
Antiviral	Acyclovir	Valacyclovir	Start with lymphodepleting chemotherapy and continue for 6–12 months or until CD4 >200 cell/mm^3

Immunosuppressive Agents Used for Treatment Of CRS/ICANS/HLH and their Associated Infection.

Immunosuppressive Therapy	Associated Infection Risk	Prophylaxis Strategy Considerations
Steroids (dexamethasone, methylprednisolone)	Well-known association with fungal infections, viral reactivations, and PJP, which is also noted in some cohorts after CAR T-cell therapy (11, 16, 22, 35, 49, 65)	Mold active prophylaxis HSV/VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation and strong consideration of pre-emptive therapy
IL-1 Receptor antagonist (anakinra)	Well tolerated with extended treatment in the rheumatoid arthritis population (106); no specific association with infectious risk in limited experience after CAR-T (107) In combination with steroids, the risk of infection may be higher (106)	If being administered with steroids, above considerations apply
IL-6 receptor antagonist (tocilizumab, siltuximab)	Safety profile post CAR-T infusion is unclear; in one report, use was associated with infections and death (108). In other populations, it has been associated with tuberculosis (TB), other mycobacterial infections, and fungal infections (39)	Mold active prophylaxis HSV prophylaxis if seropositive CMV preemptive therapy Weekly monitoring for viral reactivation Bacterial prophylaxis when ANC<500
JAK1/2 inhibitor (ruxolitinib)	Safety in CAR T-cell population unclear; associated with higher rates of VZV infection and hepatitis B reactivation (109, 110) in hematological malignancy population; also reports of disseminated TB, cryptococcal infection, toxoplasmosis, CMV disease, mold infections (109, 111).	Mold-active prophylaxis (with attention to drug-drug interactions between ruxolitiib and azoles) PJP prophylaxis VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation among those on multiple and strong consideration of pre-emptive therapy HBV prophylaxis if HBSAg+ and/or HBV DNA PCR is detectable Bacterial prophylaxis when ANC<500
Chemotherapy (etoposide)	Bacterial infections with neutropenia	Attention to bacterial prophylaxis when ANC<500
Anti-IFN-gamma monoclonal antibody (emapalumab)	Viral reactivations, fungal infections, TB reactivation and other mycobacterial infections have been reported in other populations (112, 113)	Fungal prophylaxis on case by case basis PJP prophylaxis VZV prophylaxis if seropositive Weekly monitoring for CMV reactivation and consideration of pre-emptive therapy

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Vaccines For CAR T-cell Therapy Recipients.

	Killed/inactivated vaccines	Live and non-live adjuvant vaccines
Eligibility	6 months post-CAR-T 2 months since last IGRT	1-year post-CAR-T
Contraindications	• IGRT within the past 2 months • Receiving T-cell or B-cell directed immunosuppressive therapy. • Receipt of anti-CD20 or anti-CD19 in the prior 6 months • Actively receiving chemotherapy	• Received anti-CD19 or anti-CD20 therapy within the past 6 months. • 1 year post CAR T-cell therapy • 2 years post autologous or allogeneic HCT • <1 y off of all systemic immunosuppressive therapy • < 8 months after the last dose of IGRT • Absolute CD4 count < 200 cells/mm^3 • Absolute CD19+ or CD20+ B cell count < 20 cells/mm^3 • Actively receiving chemotherapy
Vaccinations to consider	Influenza Covid-19 Pneumococcal conjugate Pneumococcal polysaccharide Diphtheria, tetanus, and acellular pertussis (DTaP) Hepatitis A virus Hepatitis B virus	Varicella Zoster Virus

- O momento ideal da vacinação não é claro, depende do tempo da reconstituição da imunidade celular e humoral após CAR-T.
- A vacina contra SARS CoV-2 pode ser iniciada no D+90 pós-infusão.
- As principais vacinas a serem consideradas incluem influenza anual, Strept. pneumoniae, Haemophilus influenza tipo B, toxinas de Corynebacterium diphtheriae e Clostridium tetani, Bordetella pertussise vírus da Hepatite A e B
- Doentes com >50ª, soropositivos para VZV ou histórico de herpes zóster, a vacina zóster recombinante (Shingrix) deve ser considerada

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