

VIII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

Vigo, 19 y 20 de febrero de 2026



Toxicidades: un reto

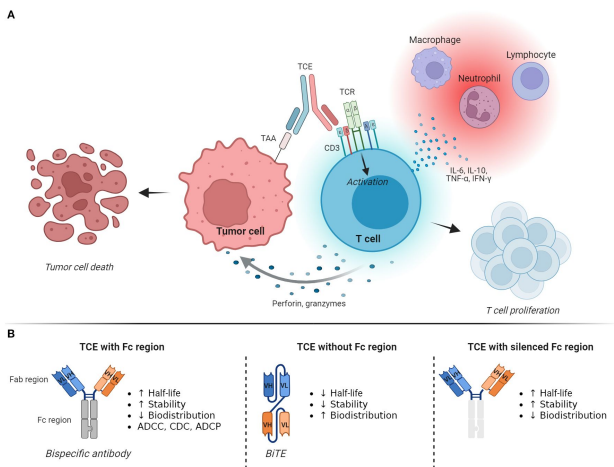
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Conflictos de interés

Consultant or Advisory Role: GSK, Sanofi, Pfizer, BMS, MSD

Speaking: AZ, GSK, MSD, Sanofi, Pfizer, BMS

INTRODUCCIÓN



Relationship with dose intensity

Incidence (moderate/severe AEs)

Variability of AE profile

Affected systems/organs

Time course

Predictability

Immune checkpoint inhibitors

T-cell engagers

Immune-related adverse events	Reactions and adverse events with T-cell engagers
Quite unrelated	Highly related
Majority without	Majority with
Highly variable	Constant profile
Any organ affected	Mainly CRS and neurological events
Very variable, even after end of therapy	Mostly during step-up dosage or just beyond
Largely unpredictable	Quite predictable

Síndrome de liberación de citoquinas

50-90%

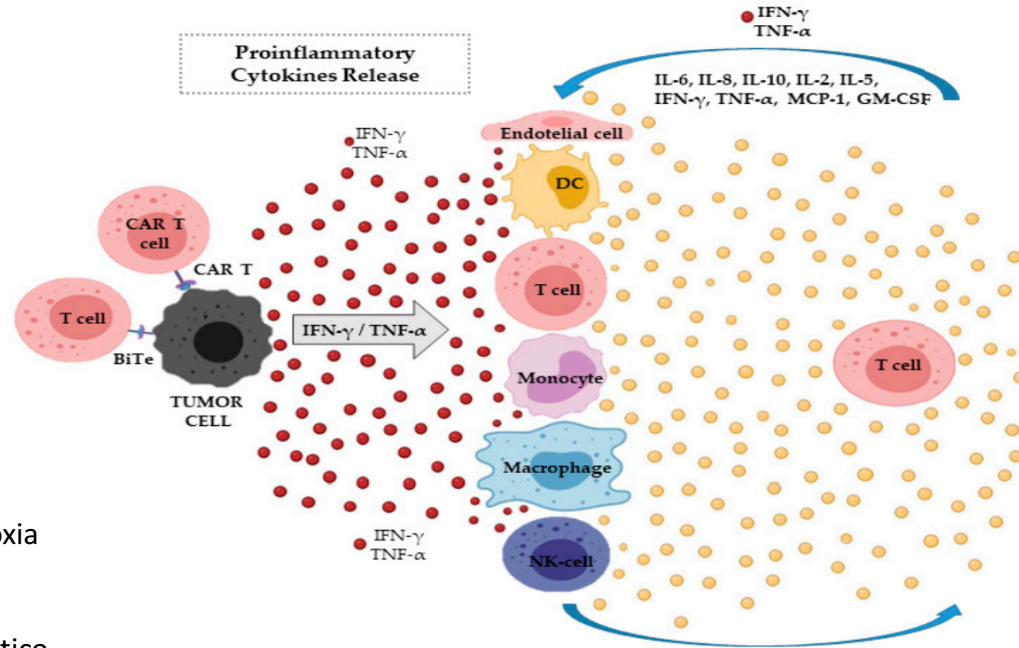
Mayoría grado 1-2
Errores en el reporte

Sobreproducción de citoquinas:

IL6
IL1, IL15, IFNgamma, TNFalfa

Daño endotelial >>> hipotensión, hipoxia

Daño cardíaco, gastrointestinal y hepático



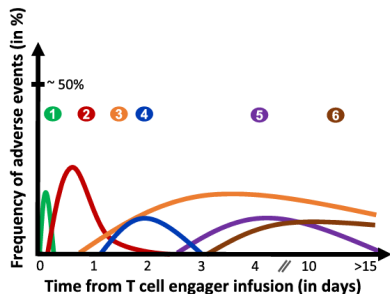
Síndrome de liberación de citoquinas

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, non-rebreather mask, or venturi mask	Requiring positive press CPAP, BiPAP, intubation mechanical ventilation)

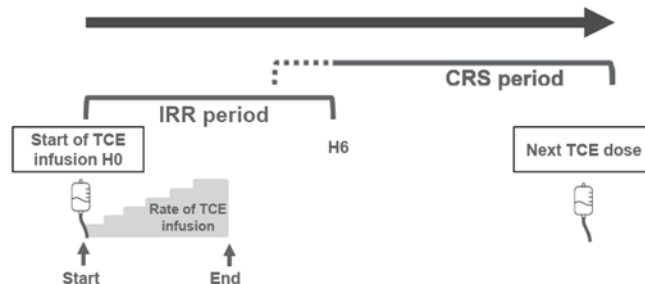
Síndrome de liberación de citoquinas

Expected timing for reactions and adverse events with T-cell engagers

- 1 IRR
- 2 CRS
- 3 Infections
- 4 Tumor flare reaction
- 5 ICANS
- 6 Cytopenia



IRR and CRS period definitions



IRR

Immediate reaction or within 6 hours of the start of the infusion, typically of an **immunoallergic** nature, mostly chills and flushing, skin, nausea and respiratory reaction generally afebrile.

CRS

Febrile reaction and which can be accompanied by hypotension and/or hypoxia, generally occurring beyond the 6 hours following the start of treatment and in connection with **the pharmacodynamics** of the treatment, and mainly IL-6 driven.

HLH

Severe reaction typically revealed by **febrile cytopenia** and biological abnormalities (hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia) and which can be accompanied by **organ failures**, and generally following a cytokine release syndrome, and both IL-1 and IL-6 driven.

Síndrome de liberación de citoquinas

Prevención

Logísticas

- Acceso a UCI
- Disponibilidad Tocilizumab
- Administración temprana
- Vigilancia estrecha step-up
- Valorar ingreso (primeras dosis)
- Formación personal

Profilaxis

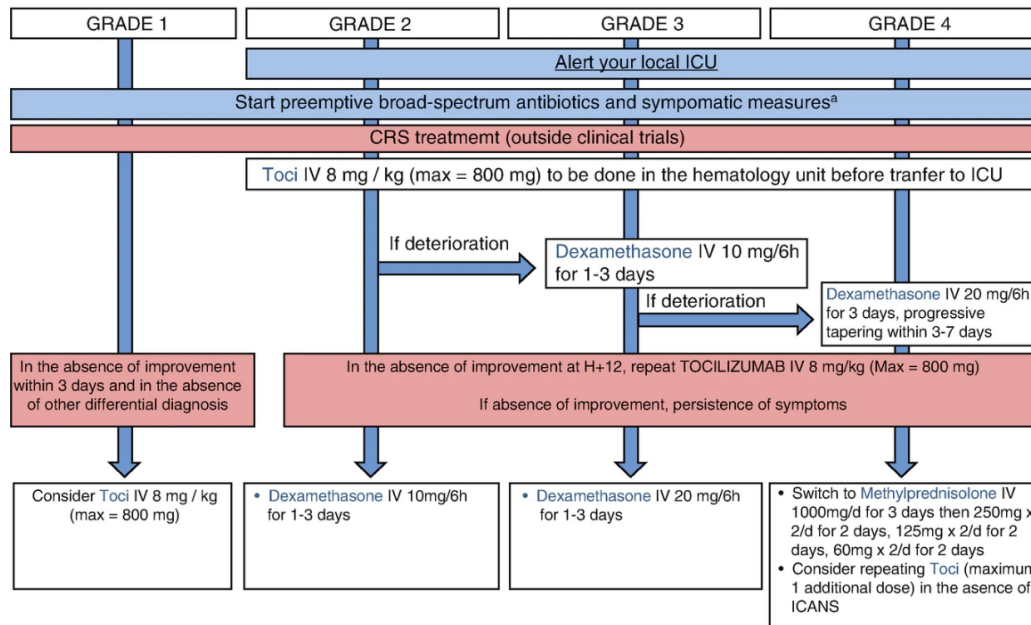
- Volumen previo (1 litro 3-5 horas antes)
- Dexametasona 4-10 mg dexta (especialmente si previo o primeras dosis)
- Antipiréticos
- Valorar reducir o eliminar en ciclos posteriores

Educación

- Hidratación posterior
- Signos y síntomas de alarma
- Pacientes alto riesgo (carga tumoral, progresión rápida, comorbilidades)

Síndrome de liberación de citoquinas

Tratamiento

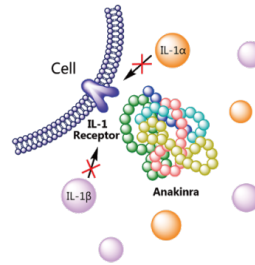


Síndrome de liberación de citoquinas

Tratamiento (refractarios)

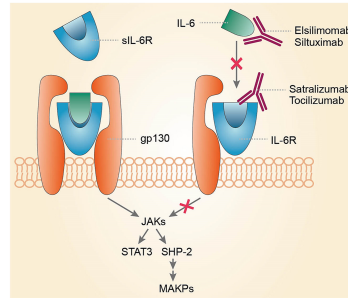
Antagonista del receptor alfa de IL1 (Anakinra)

- Artritis reumatoide (FDA/EMA)
- Síndrome activación macrófagica
- 100 mg cada 6 horas (subcutáneo)



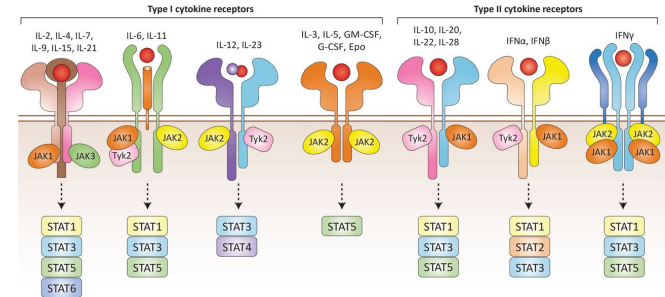
Siltuximab: antiIL6

- No provoca pico de IL6
- Afectación SNC
- Más afinidad



Inhibidores de la vía JAK

Anti IFN gamma?



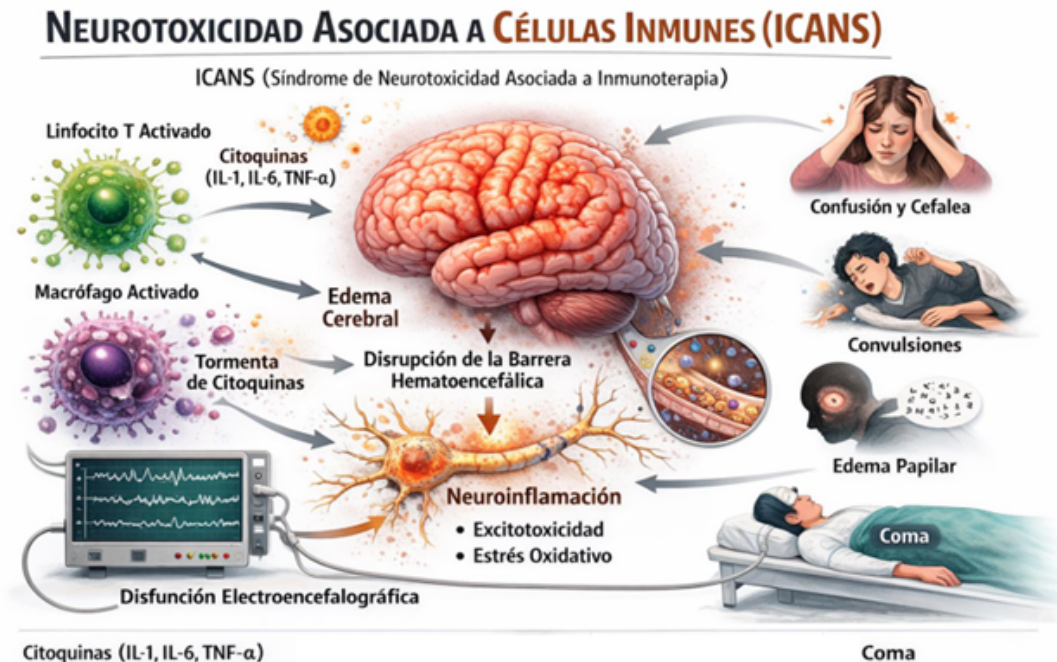
ICANS (Immune effector Cell associated Neurotoxicity)

10-15%

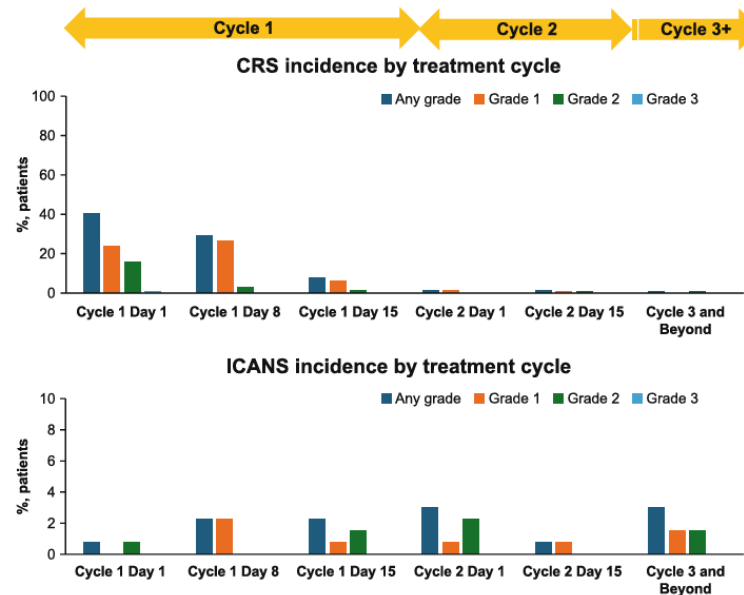
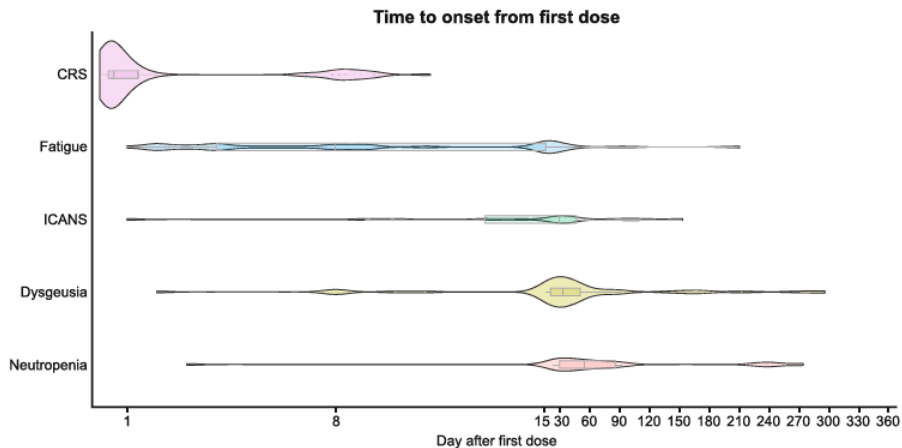
3-5% graves

Posible relación con antígeno (TAA)
DLL3-cerebro sano

- Citoquinas proinflamatorias
- Células bystander (MF)
- Alteración endotelio vascular



ICANS (Immune effector Cell associated Neurotoxicity)



ICANS (Immune effector Cell associated Neurotoxicity)

Escala ICE

		Puntos		Tareas
1	ORIENTACIÓN	4	✓	<ul style="list-style-type: none"> • Año • Mes • Ciudad • Hospital
2	NOMINAR	3	✓	<ul style="list-style-type: none"> • Reloj • Bolígrafo • Botón
3	ÓRDENES	1	✓	<ul style="list-style-type: none"> • Cierre los ojos
4	ESCRITURA	1	✓	<ul style="list-style-type: none"> • Escriba una frase
5	ATENCIÓN	1	✓	<ul style="list-style-type: none"> • Sustraer de 10 en 10 desde 100

Date / time	Year	Month	City	Hospital / Place	Follow command	Object 1	Object 2	Object 3	Serial 10s	Handwriting	Score	Grade
10/3/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motor bikes and a jet ski											
13/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
14/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
14/01/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4/10	
Staff initials	Sentence EEG / NA											
Staff initials	Sentence [redacted] in a [redacted] [redacted]											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4/10	2
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4/10	3
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4/10	3
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											
17/1/23	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	4/10	3
Staff initials	Sentence I have 3 dogs, 3 cars, 3 motorbikes and a jet ski											

7-9 puntos: ICANS grado 1

3-6 puntos: ICANS grado 2

0-2 puntos: ICANS grado 3

ICANS (Immune effector Cell associated Neurotoxicity)

Evaluación neurológica:

Imagen: MRI/CT

EEG: lentificación: lentificación generalizada del fondo, ritmo anormal, patrones de descargas periódicas

Fondo de ojo

Valorar PL: descartar causa infecciosa, carcinomatosis

Hospitalización (aviso a UCI)

Medidas anti-aspiración: elevación de cama, limitar ingesta oral

Si HTIC: acetazolamida, manitos...)

ICANS (Immune effector Cell associated Neurotoxicity)

Neurotoxicity Domain ^{aa}	Grade 1	Grade 2	Grade 3	Grade 4
ICE score ^{bb}	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness ^{cc}	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging ^{dd}	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

UCI

Grado 1

- Tratamiento de soporte

Grado 2

- Dexametasona 10 mg
- Repetir cada 6-12 horas

Grado 3

- Dexametasona 10 mg cada 6 horas
- Valorar suspensión

Anakinra 100 mg c 6 horas

Grado 4

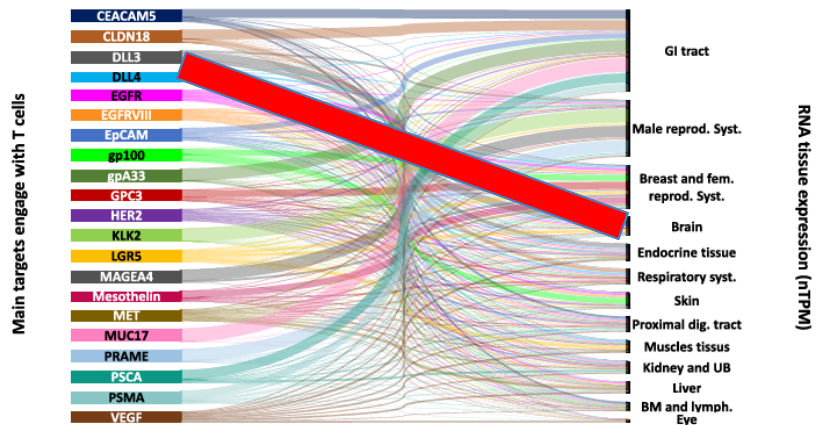
- Metilprednisolona 1000 mg/día x 3 días
- Tapering rápido
- Suspensión definitiva

Anakinra 100 mg c 6 horas

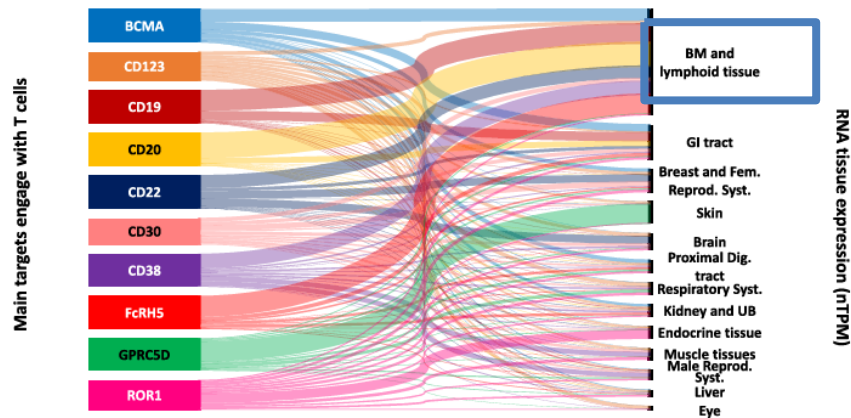
Asociar terapia antiIL6 si CRS

Otras toxicidades

Solid tumors targets engaged by bi-specifics and their tissue expression RNA




Hematological cancer targets engaged by bi-specifics and their tissue expression RNA



On target/off tumor

Otras toxicidades

	Infections	Tumor flare reactions	Cytopenia
Typical expected time of occurrence	1-14 days after infusion	1-3 days after infusion	3-14 days after infusion
Main sign and symptoms	Fever, chills, viral or bacterial infections signs	Tumor pain, effusion worsening, tumor compression signs and symptoms.	Neutropenia, anemia, thrombocytopenia related symptoms.
Pathophysiology aspects	On target effect in immune component	Tumor microenvironment inflammation	Direct toxicity on hematopoietic precursor (mainly TCE for blood cancer)
Main drugs interventions	Anti-infectious agents to treat infection. Prevention and pre-emptive measures are important with prophylaxis, vaccinations, gammaglobulins in severe cases with humoral deficiency	Corticosteroids, analgesic	Stimulating factors (GCSF) for neutropenia

DeLLphi-301		
Adverse Events	Observations	Patient Management
 Dysgeusia	<ul style="list-style-type: none"> Dysgeusia incidence = 32% Median time to onset: 34 days (IQR, 21 – 51) 	<ul style="list-style-type: none"> Investigators used previously published strategies for managing dysgeusia including: <ul style="list-style-type: none"> Nutritional counseling by registered dietitian Maintenance of good oral dental hygiene Maintenance of adequate hydration (~ 1.5 – 2 L of water/day) Periodic chewing of cardamom; inhaling smell of cloves and lemon ≥ 2x/day for ~15 seconds

Conclusiones

- No hay un consenso aceptado en el manejo de las toxicidades de los T-cell engagers
- Las toxicidades asociadas a los T-cell engagers exige un enfoque multidisciplinar, protocolos estandarizados y una vigilancia estrecha
- El manejo del CRS debe ser precoz y protocolizado y requiere estrategias preventivas estructuradas
- La neurotoxicidad (ICANS) no es tan frecuente pero puede ser grave, por lo que exige monitorización neurológica y tratamiento basado en corticoides.
- Las reacciones on-target/off-tumor, reflejan la complejidad biológica de los T-cell engagers y requieren una vigilancia clínica rigurosa para detectarlas precozmente

Gracias

