Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Monica Galli

Complicanze neurologiche delle CAR-T

Nothing to disclose

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

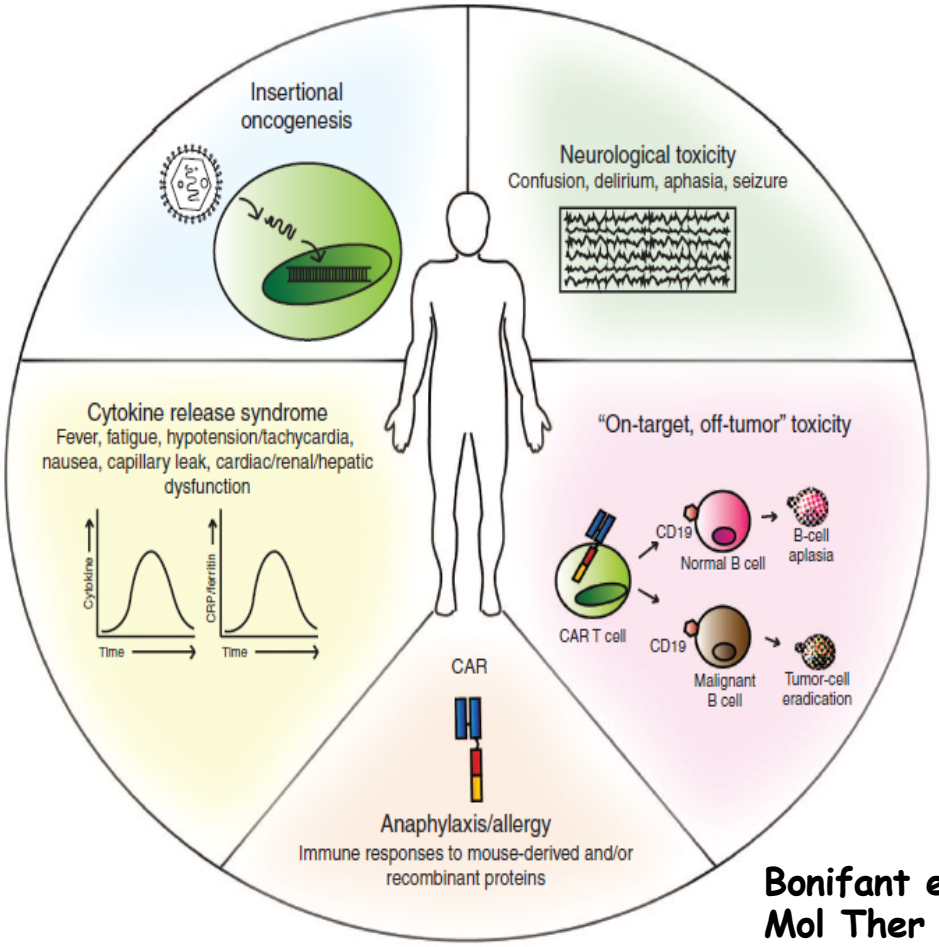
CAR-T Neurotoxicity - Definitions

CRES: CAR-related encephalopathy syndrome

ICANS: Immune effector cell-associated neurotoxicity syndrome

Lee et al. BBMT 2019;25:625

CAR-T Cells Toxicities

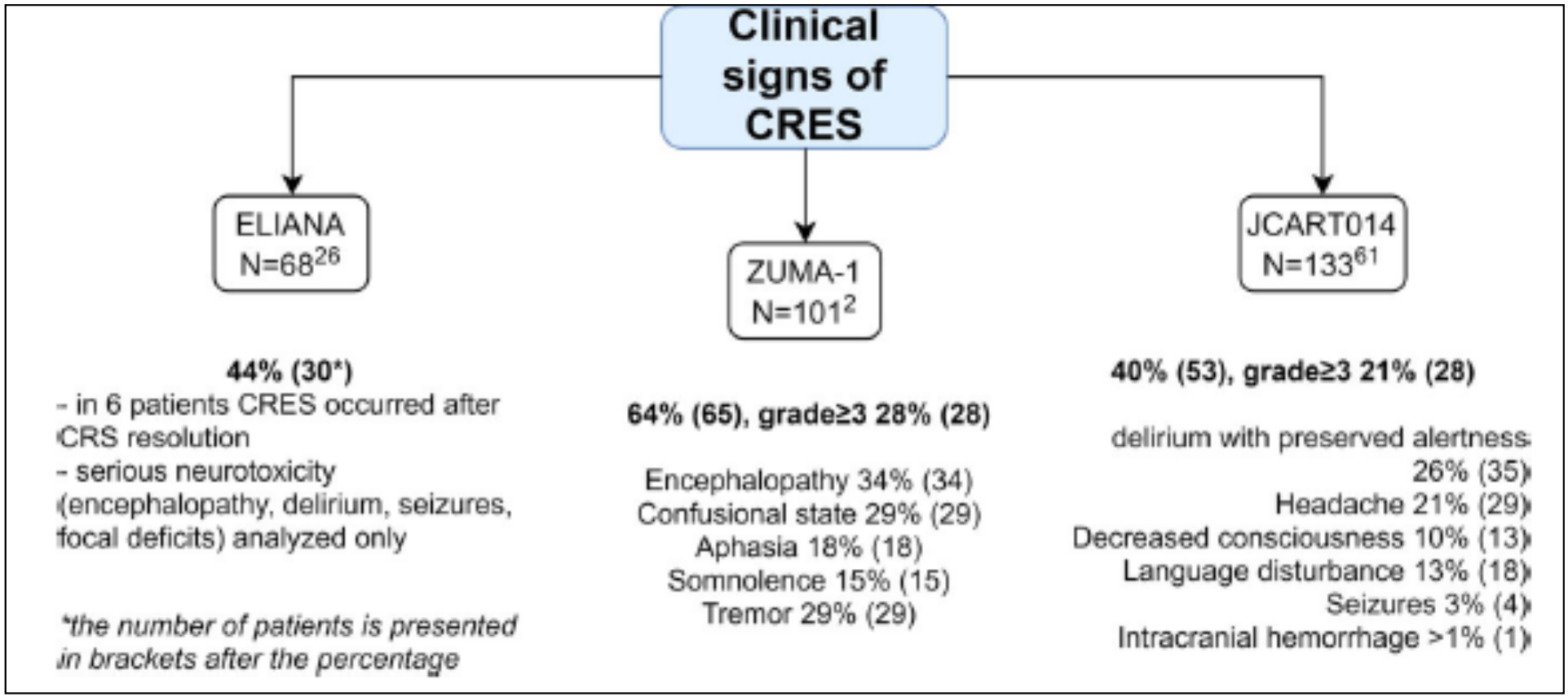


Bonifant et al.
Mol Ther - Oncolytics 2016;3:16011

- Lymphodepletion regimen
- Antigen type/epitope
- CAR generation
- T-cell subpopulation composition
- CAR-T cell dose & expansion peak
- Disease type
- Tumor burden

Titov et al. Cell Death & Dis 2018;9:897

CAR-T Cells Toxicities



Titov et al. Cell Death & Dis 2018;9:897

Neurotoxicity - Pathophysiology

Two hypotheses for CRES:

1. **Passive infusion of cytokines into the brain**

2. **Trafficking of T-cells into the CNS**

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

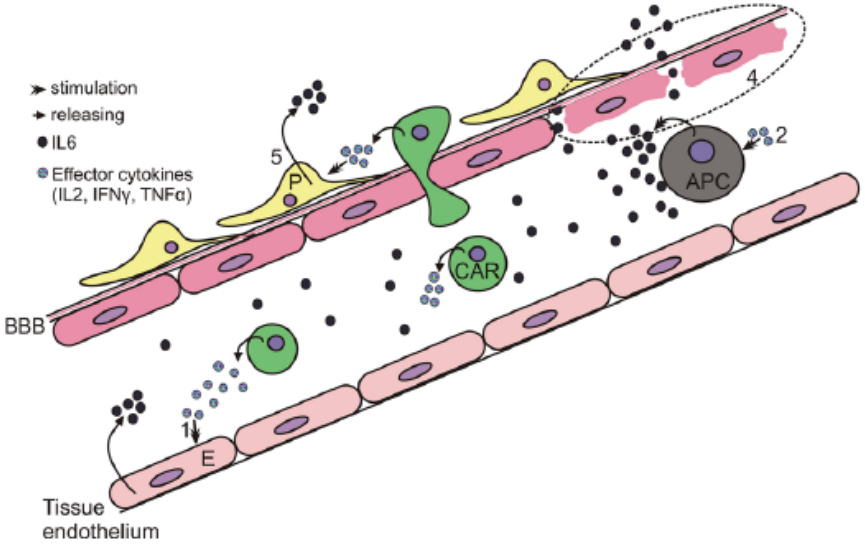
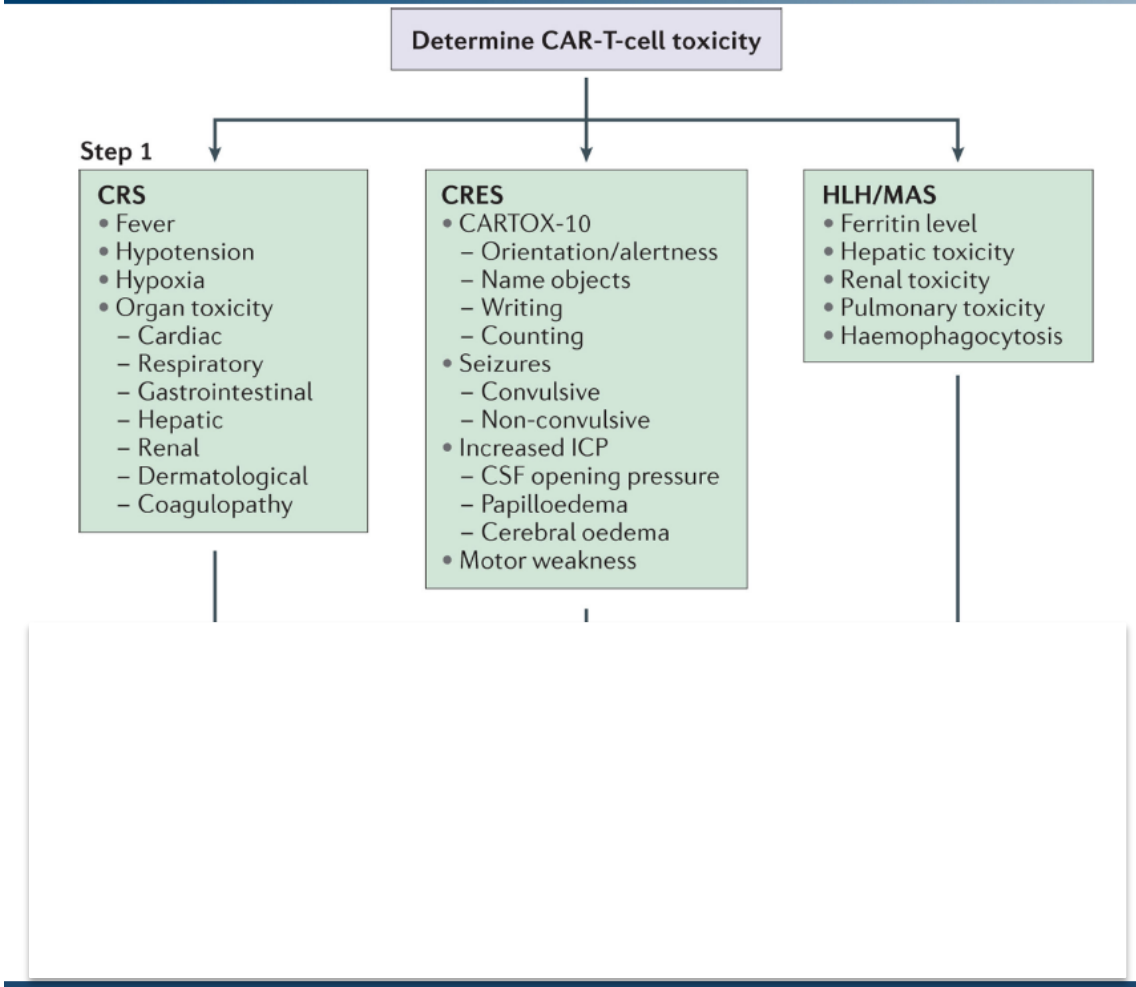


Fig. 2 Pathogenesis of CRS and CRES. Activated CAR T-cells (CAR, green) release effector cytokines that in turn activate (1) Endothelial cells (E, pink) and (2) Antigen-presenting cells and macrophages (APC, gray). These cells produce IL6 driving CRS onset. (3) CAR-T cells are able to penetrate the blood–brain barrier (BBB). All the above-mentioned as well as other factors (see CRES pathogenesis) probably contribute to the BBB disruption and the passive passage of cytokines into the CNS (4) resulting in CRES. Pericytes (P, yellow) as well as endothelial cells exposed to effector cytokines produce IL6 (5) driving CRES further

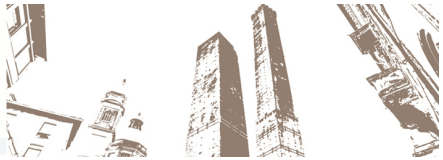
Titov et al. Cell Death & Dis 2018;9:897

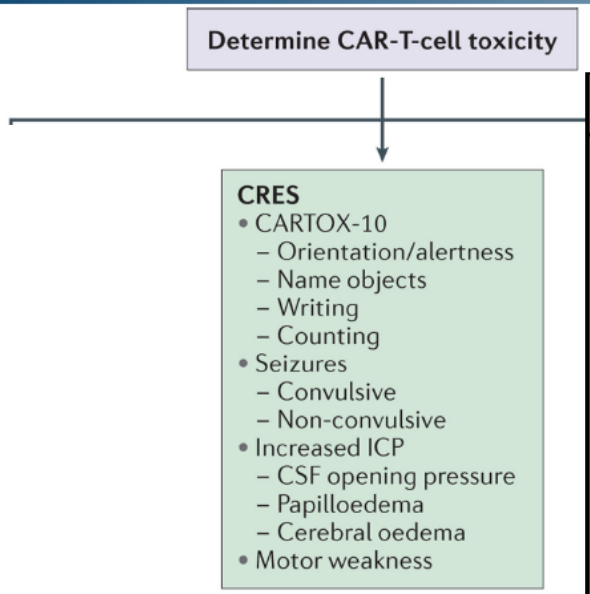
Neurotoxicity – 3 Steps Assessment



Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Neurotoxicity – 3 Steps Assessment





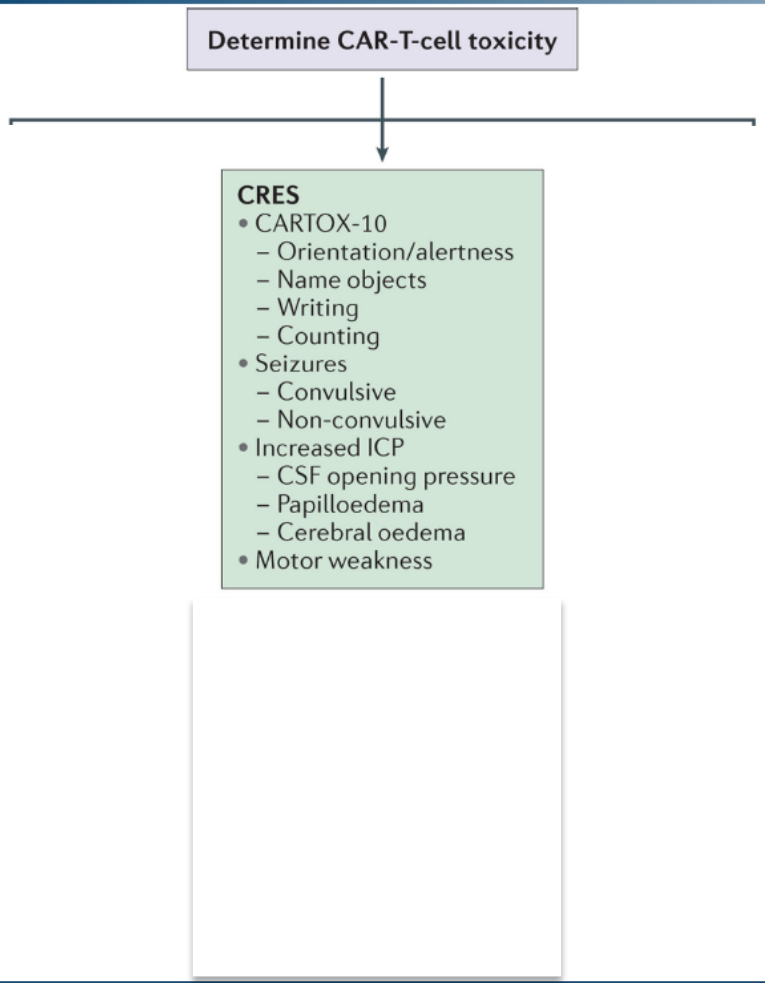
CARTOX-10 [12]

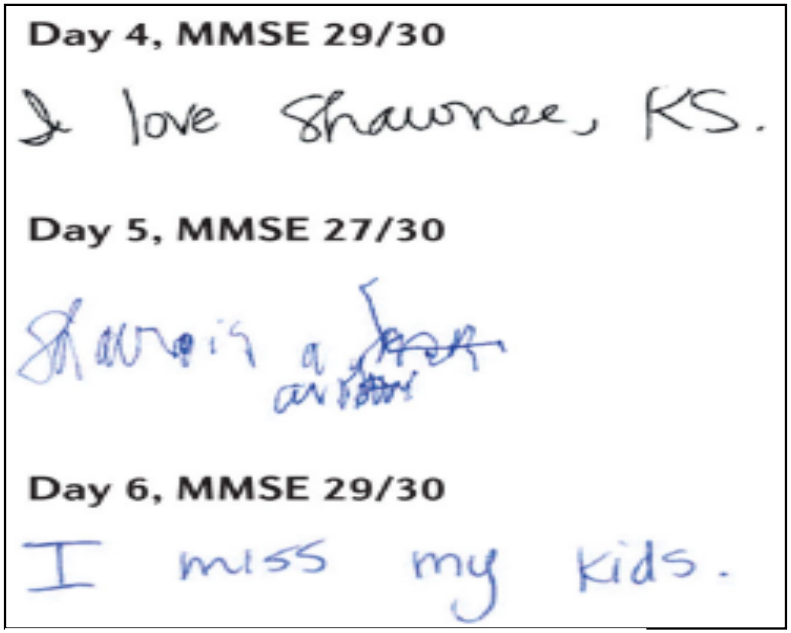
- **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

Lee et al. BBMT 2019;25:625

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Neurotoxicity – 3 Steps Assessment

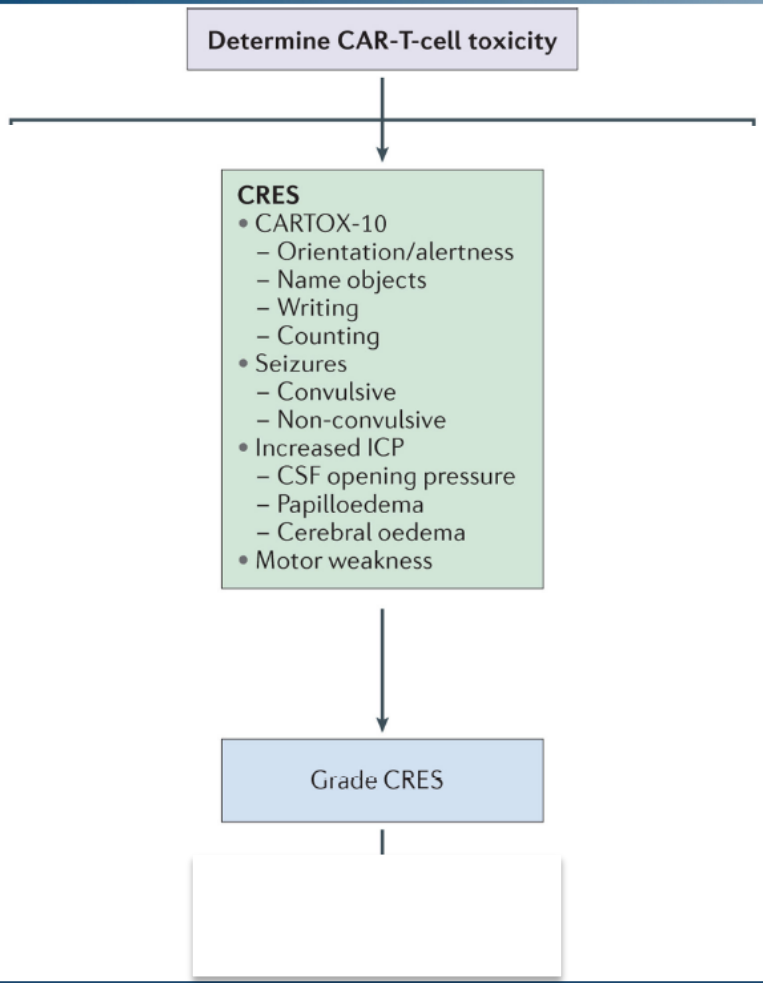




MMSE:
mini mental status exam

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Neurotoxicity – 3 Steps Assessment



Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Encephalopathy Assessment Tools

Lee et al. BBMT 2019;25:625

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points	• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points	• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point	• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point	• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
	• **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.

Scoring: 10, no impairment;
7-9, grade 1 ICANS;
3-6, grade 2 ICANS;
0-2, grade 3 ICANS;
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS.

CAR-T Neurotoxicity - Grading

Symptom or sign	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score (by CARTOX-10 *)	7–9 (mild impairment)	3–6 (moderate impairment)	0–2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks
Raised intracranial pressure	NA	NA	Stage 1–2 papilloedema‡, or CSF opening pressure <20mmHg	Stage 3–5 papilloedema‡, or CSF opening pressure ≥20 mmHg, or cerebral oedema
Seizures or motor weakness	NA	NA	Partial seizure, or non-convulsive seizures on EEG with response to benzodiazepine	Generalized seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness

CAR, chimeric antigen receptor; CARTOX-10, CAR-T-cell-therapy-associated toxicity 10-point neurological assessment CSF, cerebrospinal fluid;

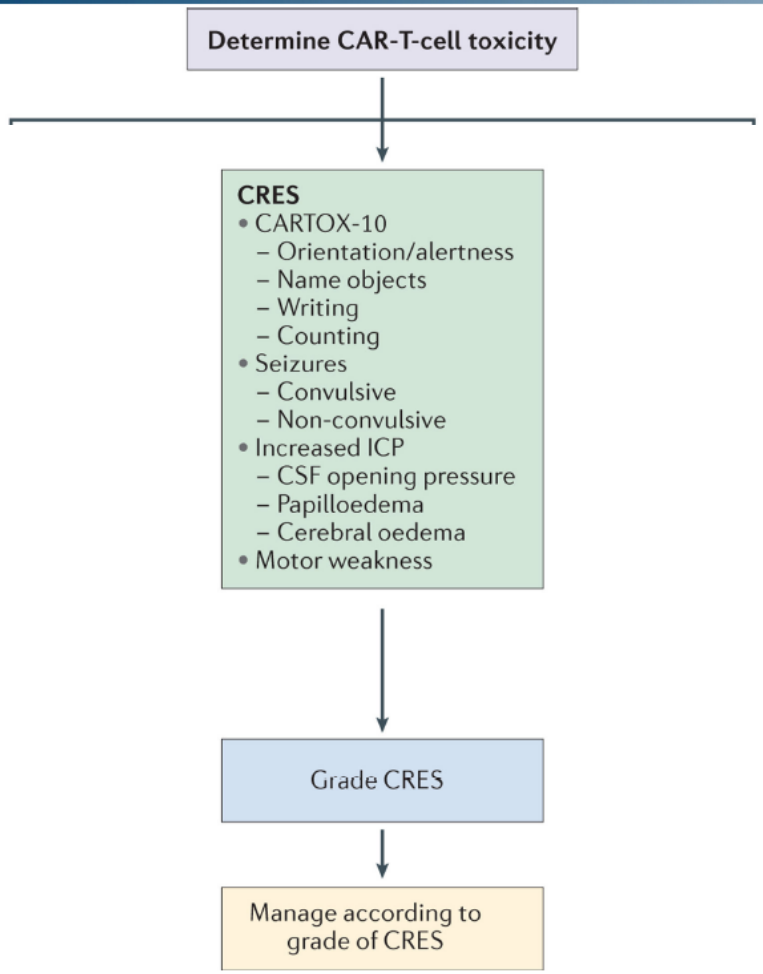
EEG, electroencephalogram; NA, not applicable.

* In the CARTOX-10, one point is assigned for each of the following tasks that is performed correctly (normal cognitive function is defined by an overall score of 10): orientation to year, month, city, hospital, and President/Prime Minister of country of residence (total of 5 points); name three objects — for example, point to clock, pen, button (maximum of 3 points); write a standard sentence, for example, 'our national bird is the bald eagle' (1 point); count backwards from 100 in tens (1 point).

‡ Papilloedema grading is performed according to the modified Frisén scale[98].

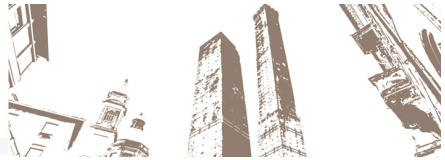
Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Neurotoxicity – 3 Steps Assessment



Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Neurotoxicity - Recommendations



Grade 1

- Vigilant supportive care; aspiration precautions; intravenous (IV) hydration
- Withhold oral intake of food, medicines, and fluids, and assess swallowing
- Convert all oral medications and/or nutrition to IV if swallowing is impaired
- Avoid medications that cause central nervous system depression
- Low doses of lorazepam (0.25–0.5 mg IV every 8 h) or haloperidol (0.5 mg IV every 6 h) can be used, with careful monitoring, for agitated patients
- Neurology consultation
- Fundoscopic exam to assess for papilloedema
- MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible
- Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve; if no seizures are detected on EEG, continue levetiracetam 750 mg every 12 h
- If EEG shows non-convulsive status epilepticus, treat as per algorithm in BOX 3
- Consider anti-IL-6 therapy with tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV, if CRES is associated with concurrent cytokine-release syndrome (CRS)

Grade 2

- Supportive care and neurological work-up as described for grade 1 CRES
- Tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV if associated with concurrent CRS
- Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti-IL-6 therapy, or for CRES without concurrent CRS
- Consider transferring patient to intensive-care unit (ICU) if CRES associated with grade ≥2 CRS

Grade 3

- Supportive care and neurological work-up as indicated for grade 1 CRES
- ICU transfer is recommended
- Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 2 CRES and if not administered previously
- Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, or for CRES without concurrent CRS; continue corticosteroids until improvement to grade 1 CRES and then taper
- Stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated as per algorithm presented in BOX 4
- Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 CRES

CAR-T Neurotoxicity - Recommendations

Grade 4

- Supportive care and neurological work-up as outlined for grade 1 CRES
- ICU monitoring; consider mechanical ventilation for airway protection
- Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 CRES
- High-dose corticosteroids continued until improvement to grade 1 CRES and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days
- For convulsive status epilepticus, treat as per algorithm in BOX 3
- Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in BOX 4

All medication doses indicated are for adults. CAR, chimeric antigen receptor.
*Maximum amount of tocilizumab per dose is 800 mg

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Recommendations for Status Epilepticus

Non-convulsive status epilepticus

- Assess airway, breathing, and circulation; check blood glucose
- Lorazepam* 0.5 mg intravenously (IV), with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures
- Levetiracetam 500 mg IV bolus, as well as maintenance doses
- If seizures persist, transfer to intensive-care unit (ICU) and treat with phenobarbital loading dose of 60 mg IV
- Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 h; phenobarbital 30 mg IV every 12 h

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Recommendations for Status Epilepticus

Convulsive status epilepticus

- Assess airway, breathing, and circulation; check blood glucose
- Transfer to ICU
- Lorazepam* 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures
- Levetiracetam 500 mg IV bolus, as well as maintenance doses
- If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV
- Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 h; phenobarbital 1–3 mg/kg IV every 12 h
- Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

Recommendations for Raised Intracranial Pressure

Stage 1 or 2 papilloedema* with cerebrospinal fluid (CSF) opening pressure of <20 mmHg without cerebral oedema

- Acetazolamide 1,000 mg intravenously (IV), followed by 250–1,000 mg IV every 12 h (adjust dose based on renal function and acid–base balance, monitored 1–2 times daily)

Stage 3, 4, or 5 papilloedema*, with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg

- Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for grade 4 CAR-T-cell-related encephalopathy syndrome (CRES; BOX 2)
- Elevate head end of the patient's bed to an angle of 30 degrees
- Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 h
- Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below)
  - Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 h while monitoring metabolic profile and serum osmolality every 6 h, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40
  - Hypertonic saline: initial 250 ml of 3% hypertonic saline; maintenance at 50–75 ml/h while monitoring electrolytes every 4 h, and withhold infusion if serum Na levels reach ≥155 mEq/l
  - For patients with imminent herniation: initial 30 ml of 23.4% hypertonic saline; repeat after 15 min, if needed
- If patient has ommaya reservoir, drain CSF to target opening pressure of <20 mmHg
- Consider neurosurgery consultation and IV anaesthetics for burst-suppression pattern on electroencephalography
- Metabolic profiling every 6 h and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

Neelapu et al. Nat Rev Clin Oncol 2018;15:47

BCMA CAR-T & MM: Prevalence of Neurotoxicity in Phase 1-2 Clinical Studies

1° Author	Journal	yr	Grade 3-4
Raje	NEJM	2019	2/33
Cohen	JCI	2019	3/25
Ali	Blood	2016	1/12
Brudno	JCO	2018	4/16
Xu	PNAS	2019	Not reported
Zhao	JHO	2018	1/57

11/143 (8%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Table 2. Adverse Events, Cytokine Release Syndrome, and Neurologic Toxic Effects.

Variable	Total (N=33)		
	Any Grade	Grade 3	Grade 4
	number of patients (percent)		
Adverse event*			
Cytokine release syndrome‡	25 (76)	2 (6)	0
Neurologic toxic effect§	14 (42)	0	1 (3)

§ Data are for events occurring in the first 90 days and including the following preferred terms: bradyphrenia, brain edema, confusional state, dizziness, hallucination, insomnia, lethargy, memory impairment, neurotoxicity, nystagmus, somnolence, and tremor.

Raje et al. NEJM 2019;380:18

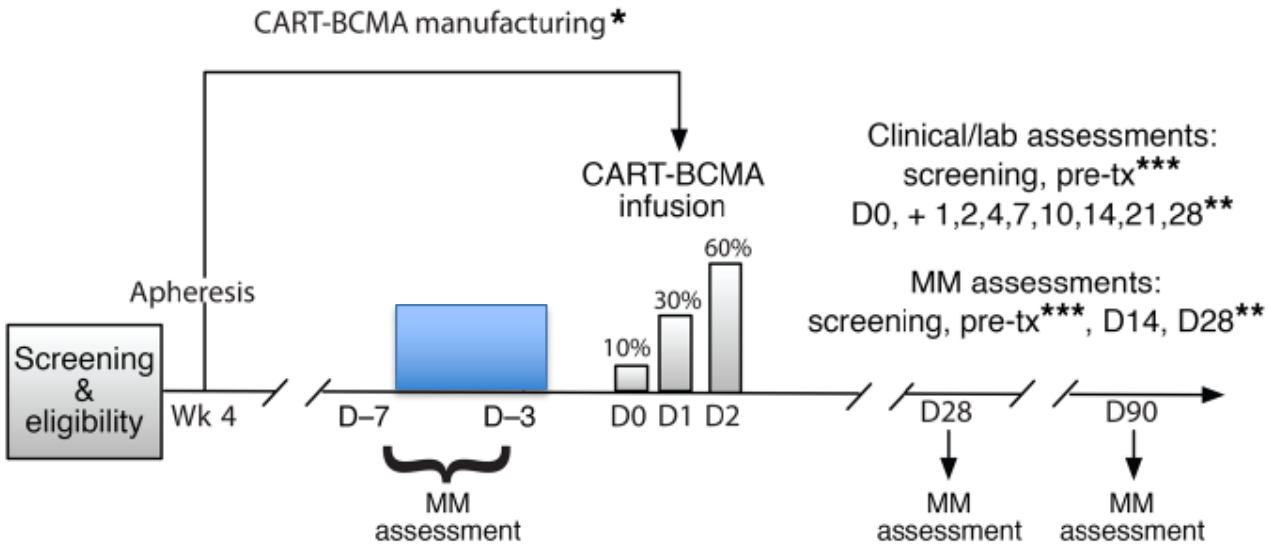
Characteristics & Management of Neurotoxicity

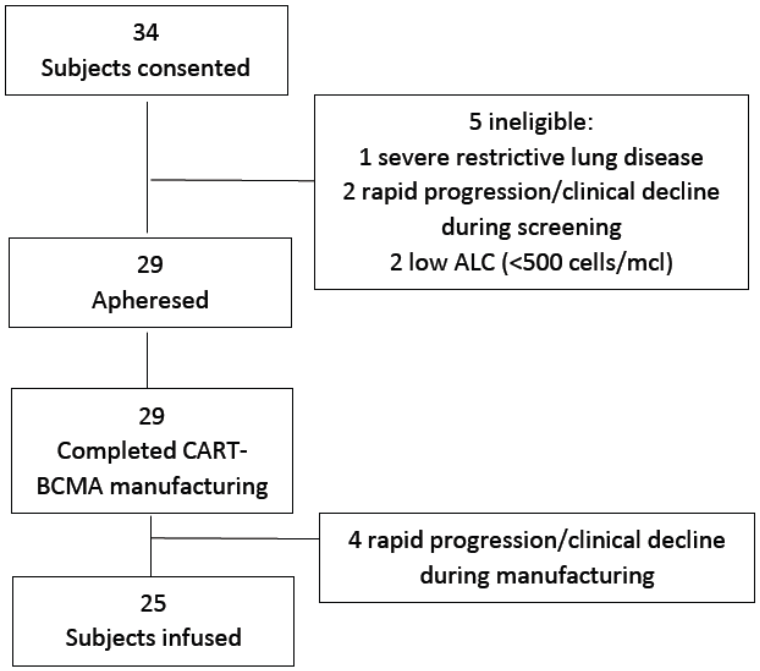
Parameter	Total (N=33)
Patients with an event—no. (%)*	
Any-grade	14 (42)
Grade ≥3	1 (3)
Median (min–max) time to onset, days	
Any-grade	5 (3–11)
First grade ≥3†	11 (11–11)
Median (min–max) duration, days	
Any-grade	8 (1–251)
Grade ≥3	22 (12–32)
Corticosteroid use—no. (%)‡	2 (6)

*Events occurring in the first 90 days and including the following preferred terms: bradyphrenia, brain edema, confusional state, dizziness, hallucination, insomnia, lethargy, memory impairment, neurotoxicity, nystagmus, somnolence, and tremor.
†Only one patient reported grade ≥3 neurotoxicity with onset at day 11.
‡Steroid doses used included dexamethasone 10 mg for treatment of grade 1 neurotoxicity and methylprednisolone 1000 mg daily for 3 days followed by a rapid taper to 250, 125 and 60 mg for treatment of the one case of grade 4 neurotoxicity.

Raje et al. NEJM 2019;380:18

B cell maturation antigen–specific CAR T cells are clinically active in multiple myeloma





Cohen et al. JCI 2019;129:2210

B cell maturation antigen–specific CAR T cells are clinically active in multiple myeloma

	Grade 1	Grade 2	Grade 3	Grade 4	All (n, %)
Neurotoxicity (total, n=25)	3	2	1	2	8 (32%)
Cohort 1 (n=9)	1	0	0	2	3 (33%)
Cohort 2 (n=5)	1	0	0	0	1 (20%)
Cohort 3 (n=11)	1	2	1	0	4 (36%)

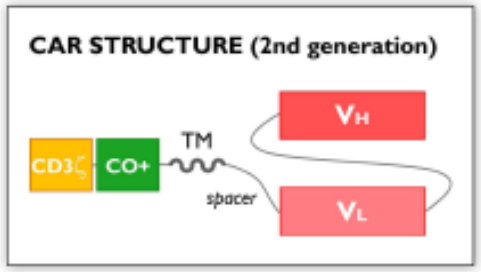
Cohen et al. JCI 2019;129:2210

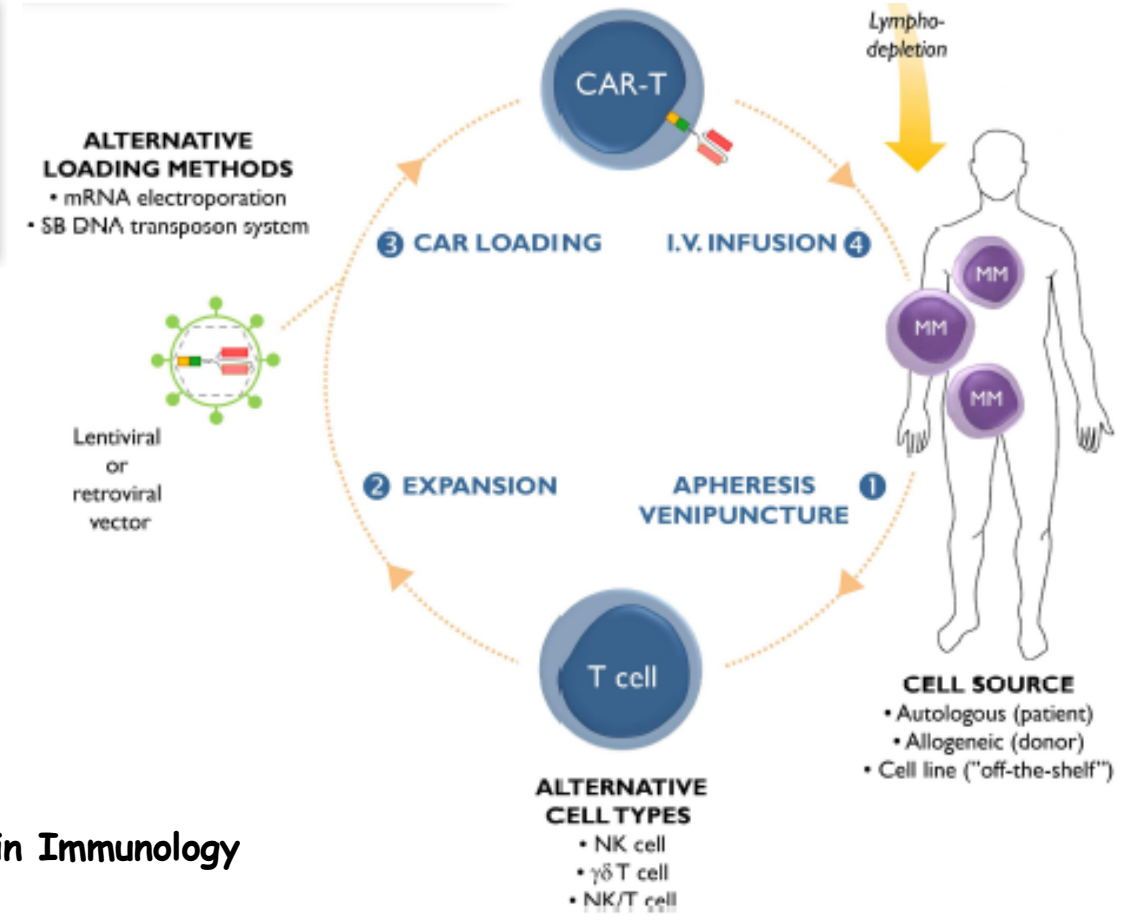
MM CAR-T other than BCMA

Antigen	Signaling domains	Cell source/type	Transfer method	Conditioning	T-cell dosage	Therapy-related side effects	Clinical effects
CD138	ND	Autologous T cells	ND	CP/Flu	1.5×10^8	• CRS gr. 2 (1)	• PR (1)
CD138	4-1BB/CD3ζ	Autologous T cells	Lentiviral	PCD, CP or VAD	0.756×10^7/kg	• Infusion-related fever (4) • Nausea and vomiting (3) • ↑ Liver function tests (1) • Possible TLS (1)	• SD > 3m (4) • ↓ circulating PCL cells (1)
CD19	4-1BB/CD3ζ	Autologous T cells	Lentiviral	HDM + ASCT	$1–5 \times 10^7$	• Hypogammaglobulinemia (1) • Autologous GvHD (1) • Mucositis (1)	• CR (1) • VGPR (6/10) at d100 post-ASCT • PR (2/10) at d100 post-ASCT
CD19 + BCMA	OX40/CD28	Autologous or allogeneic T cells	Lentiviral	CP/Flu	1×10^7/kg	• CRS gr. 1–2 (7), gr.≥3 (1) • Prolonged cytopenias (5/5) • Coagulopathy (5) • ↑ Liver function tests (4) • Pulmonary edema (3) • Pleural effusion and ascites (1)	• sCR (1/5) • VGPR (1/5) • PR (2/5) • SD (1/5)
CD19 + BCMA	OX40/CD28	Autologous T cells	Lentiviral	Bu-CP + ASCT	1×10^7/kg	• CRS gr. 1–2 (10) • Coagulopathy (7) • ↑ Troponin levels (4) • Atrial flutter (1)	• CR (7/10) • VGPR (3/10)
NKG2D ligands	CD3ζ	Autologous T cells	Retroviral	None	$1–3 \times 10^{6–7}$	• None	• None
κLC	CD28/CD3ζ	Autologous T cells	Retroviral	CP (4) or none (3)	$0.92–1.9 \times 10^8$/m²	• Lymphopenia gr. 3 (1)	• SD 6 wk–24m (4)

Timmers et al. Frontiers in Immunology 2019;10; article 1613

CAR-T & MM





ANTIGEN TARGETS

Clinical (published)
- BCMA
- CD138
- CD19
- NKG2D ligands
- Light chains

Clinical (ongoing)
- CD38
- SLAMF7/CS1
- CD44v6
- CD56
- GPRC5D
- TACI
- Lewis Y
- NY-ESO-1

Preclinical
- CD229
- Integrin β7
- CD70
- CD1d

Timmers et al. Frontiers in Immunology 2019;10; article 1613

Grazie per l'attenzione