IMPIEGO DELLE CAR-T: ATTIVITA' INFERMIERISTICHE

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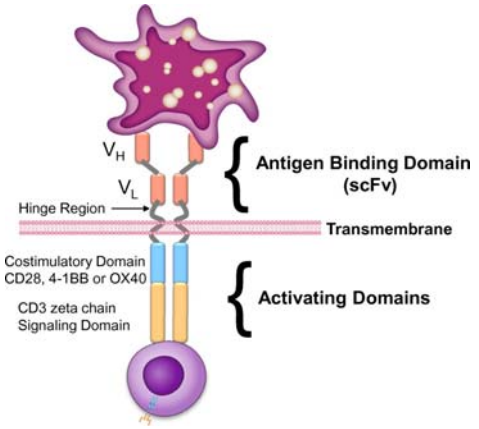
CAR-T E INNOVAZIONE

«A type of treatment in which a patient's T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells.»

- National Cancer Institute

CAR-T E INNOVAZIONE

- L'approccio con cellule T modificate per esprimere un Chimeric Antigen Receptor (CAR) è una nuova forma di immunoterapia che ha dimostrato un entusiasmante successo nel trattamento dei tumori maligni che esprimono CD19 (proteina espressa nelle cellule B) (1)
- LLA, LNH



1. Sadelain M, et al 2013

I CAR T COMMERCIALI

2017-2018: 2 prodotti CAR T cell sono stati approvati in USA (FDA) e in Europa (EMA)

- *Tisagenlecleucel* - fino a 25 aa LAL B refrattaria o in II recidiva (ELIANA trial)*
- *Axicabtagene ciloleucel*: adulti con DLBCL r/r dopo 2 o più trattamenti sistemici (ZUMA-1 trial)**

* Maude SL et al, 2018
**Neelapu SS et al, 2017

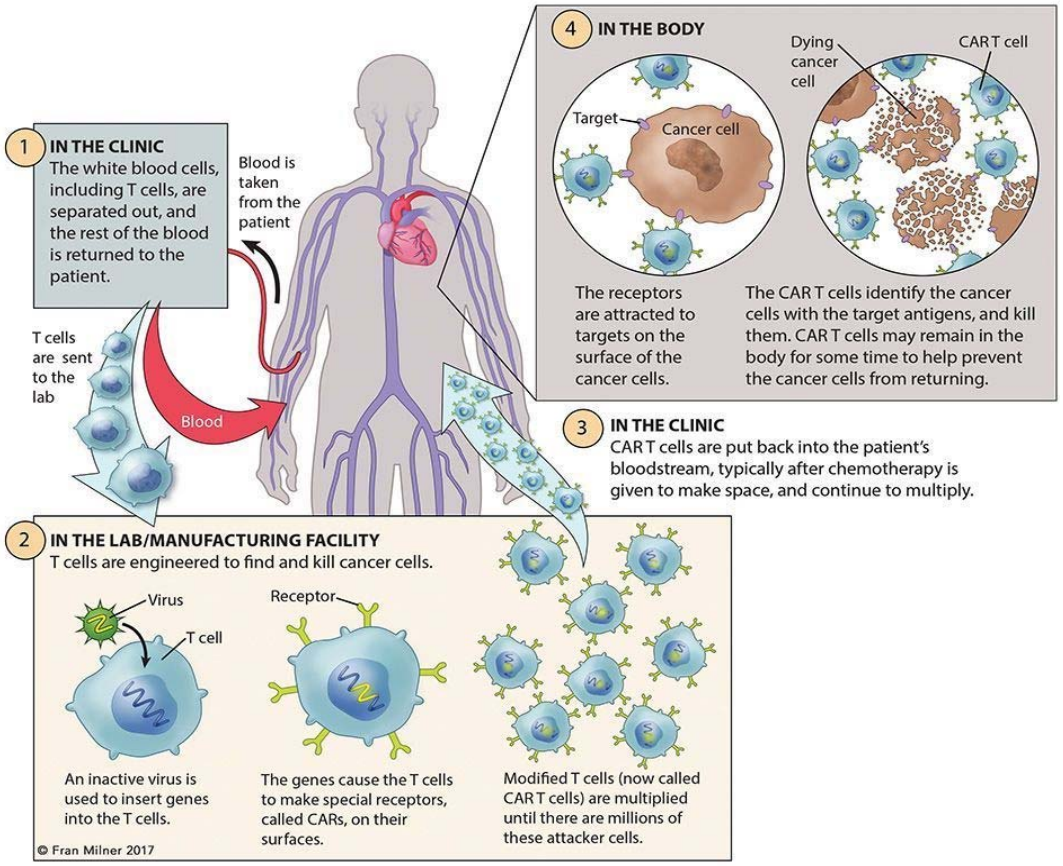
- CD19 Car T cell in LLA r/r → risposta completa ~ 90% in un singolo trials
  → ~ 70% -80% in trials multicentrico (2)
- CD19 Car T cell in LNH r/r → risposta completa ~ 50%-70% (3) (4)
- CD19 Car T cell in LLC r/r → risposta completa ~ 30%-50% (5)

2- Turtle CJ, et al, 2016
3- Sauter CS et al, 2015
4- Kochenderfer JN et al, 2015
5- Porter DL et al, 2015

DOVE SI PUO'?

CENTRI SPECIALIZZATI IN CAR T

- AREE SPECIALISTICHE (EMATOLOGIA, NEUROLOGIA..)
- TERAPIA INTENSIVA/ AREA ROSSA
- CENTRO TRASFUSIONALE / AFERESI
- ACCREDITAMENTO JACIE



IN DETTAGLIO…

1. LEUCOAFERESI: selezione delle cellule T del paziente
2. LAB: geneticamente modificati con l'introduzione di un virus non patogeno capace di produrre un recettore CAR
3. LINFODELPLEZIONE: ciclofosfamide e fludarabina
4. INFUSIONE delle cellule Car T

CRITERI DI ELEGGIBILITA’

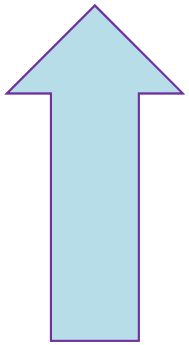
CRITERI DI INCLUSIONE

- LLA, LNH..
- Età (1-50 anni)
- Adeguata funzionalità degli organi
- Refrattari ai protocolli convenzionali (>2)

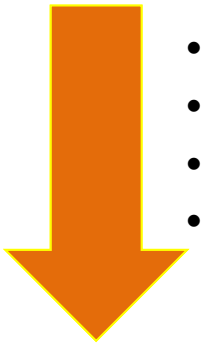
CRITERI DI ESCLUSIONE

- Iperleucocitosi
- Progressione rapida della malattia
- HBV, HCV, HIV
- Utilizzo di steroidi e anti neoplastici 2 settimane prima dell’aferesi
- Nessuna terapia immunosoppressiva attiva
- Nessuna tossicità attribuita alle terapie precedenti

VANTAGGI E SVANTAGGI

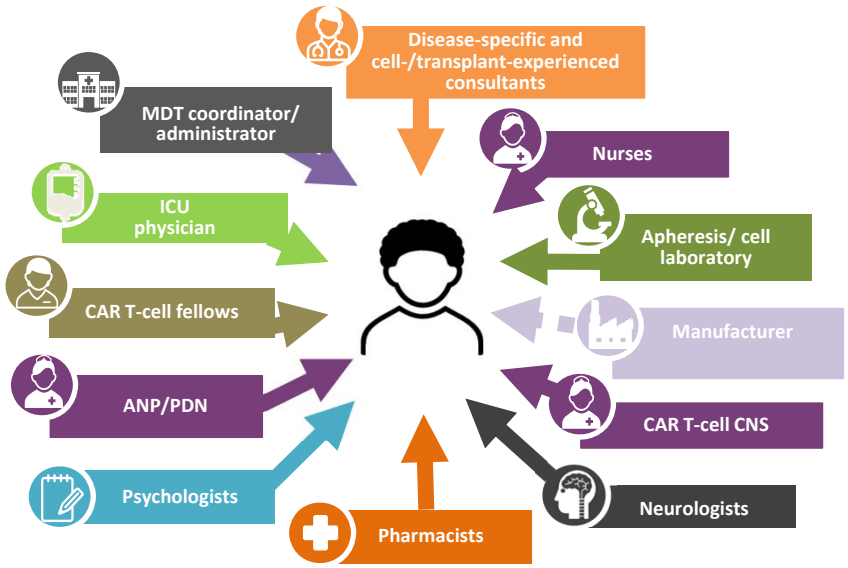


- Unica opportunità terapeutica
- Possibilità di aumentare l'efficacia e ridurre la tossicità di CAR-T modulando l'azione dei linfociti T
- Altre patologie oncologiche



- Efficacia <100%
- Tempo di produzione (4 settimane)
- Tossicità acuta anche grave (NTX, CRS)
- Costi elevati

CAR T TEAM



...nuovo staff

...meeting con il team CAR-T

...staff training

… percorsi interdisciplinari

CONSIDERAZIONI INFERMIERISTICHE: PRE CAR-T

1. Valutazione di eleggibilità (trial/ prodotto)
2. Considerare: caregiver, stato della malattia, tossicità al trattamento precedente
3. Comunicazione

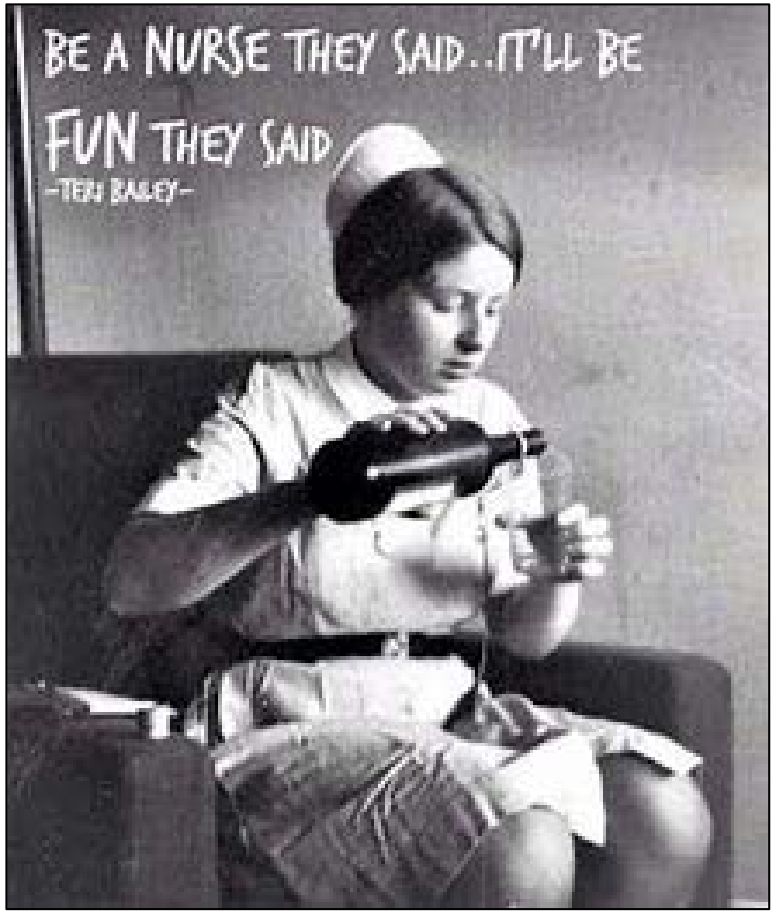
INFORMAZIONE DEL PAZIENTE

Rischi e benefici correlati a:

- Leucoaferesi
- Terapia linfo-depletiva
- Cytokine release syndrome (CRS)
- Neurotossicità (NTX)
- Supporto intensivo

SFIDE INFERMIERISTICHE

- Conoscere e gestire le tossicità
- Competenza e conoscenza dell'aferesi /lab. di cellule staminali/ BMT
- Follow-up


BE A NURSE THEY SAID..IT'LL BE
FUN THEY SAID
-TERI BAILEY-

AFERESI

- Valutazione dell'accesso venoso centrale
- Assicurare un adeguata conta linfocitaria
- Esami virologici
- Cessazione terapie precedenti

LINFODEPLEZIONE

- Solitamente 3 giorni
- Pazienti in DH o in ricovero
- Accesso venoso centrale
- Neutropenia/ sepsi

NURSING CARE E L'INFUSIONE DELLE CELL CAR-T

1. Monitoraggio continuo dei PV
2. Premedicazione: antiemetico, antistaminico (NO STEROIDI)
3. Durata dell'infusione
4. Tocilizumab presente nell'UO
5. Documentazione clinica indispensabile anche per i protocolli TRIALS

REAZIONI DURANTE L'INFUSIONE

- Non comuni
- Solitamente relative al DMSO (dimetilsolfossido)
- Alterazione dei parametri vitali
- Comunicare al medico i sintomi manifestati
- NO STEROIDI (solo se salvavita)

NURSING CARE POST CAR-T CELL

- ✓ Monitoraggio dei PV
- ✓ Valutazione della neurotossicità
- ✓ Valutazione della CRS
- ✓ Esami ematici giornalieri (includendo la ferritina)
- ✓ CMV/ADV
- ✓ Attento controllo del bilancio idrico
- ✓ Peso giornaliero

TOSSICITA’

- **Cytokine release syndrome (CRS)**
- **Neurotossicità (NTX)**
- Aplasia B-cellulare
- Haemofagocitic linphohistocytosis (HLH)

CYTOKINE RELEASE SYNDROME (CRS)

«CRS is a condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T cells, caused by a large, rapid release of cytokines into the blood from immune cells »

- The National Cancer Institute

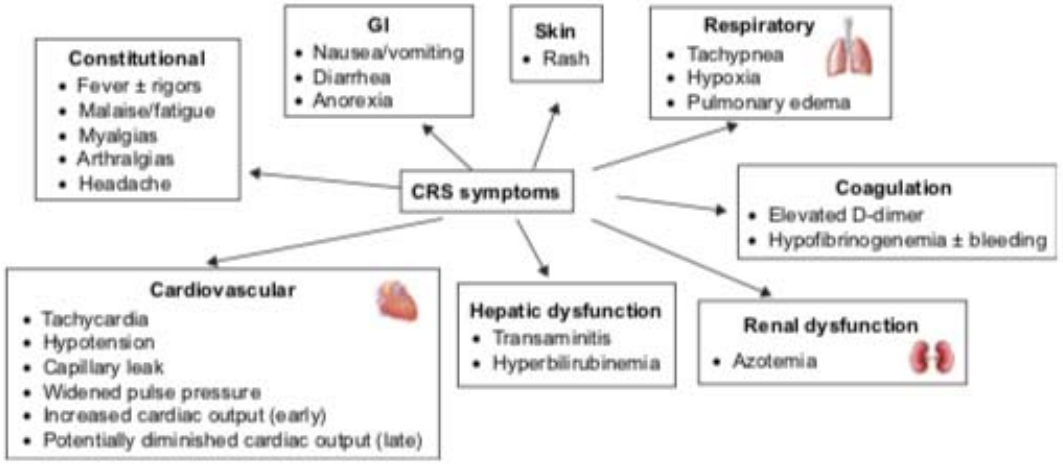


Figure 1 Symptoms of CRS.
Notes: CRS affects a number of organ systems. It requires fever at a minimum but is frequently associated with any of the symptoms shown. Additional manifestations may also rarely occur.
Abbreviations: GI, gastrointestinal; CRS, cytokine release syndrome.

SINTOMI DI CRS

CRS è una costellazione di sintomi che possono andare dal lieve e moderato al severo

- Febbre: dopo 24 ore dall'infusione per diversi giorni
- Mialgia
- Cefalea
- Nausea
- Anoressia e fatigue

sCRS : ≥ Grado 3 Penn/ Lee

- Ipotensione
- Vascular leak correlata alla compromissione respiratoria
- Insufficienza Renale
- Coagulopatia
- Encefalopatia e convulsioni

- Maude, Frey et al 2014

LEE GRADING SCALE

Table 2 CRS grading system developed by Lee et al

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: 1. Oxygen requirement <40% FiO_2 OR 2. Hypotension responsive to IV fluids or low dose of one vasopressor OR 3. Grade 2 organ toxicity	Symptoms require and respond to aggressive intervention: 1. Oxygen requirement ≥40% FiO_2 OR 2. Hypotension requiring high dose or multiple vasopressors OR 3. Grade 3 organ toxicity or grade 4 transaminitis	Life-threatening symptoms: 1. Requirement for ventilator support OR 2. Grade 4 organ toxicity (excluding transaminitis)	Death

Notes: Organ toxicities refer to CTCAE version 4.03. Reprinted from Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188–195.[9]

Abbreviations: CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous.

TRATTAMENTO DELLA CRS IN CAR T CELL

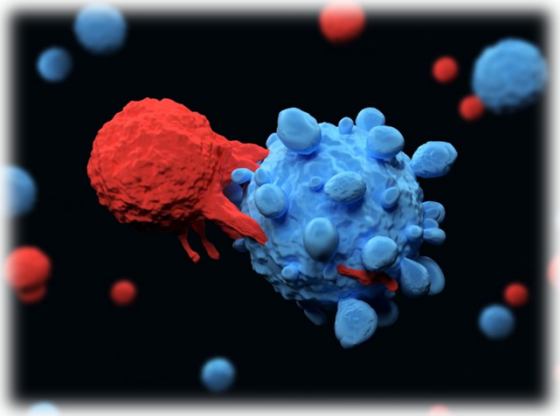
- ✓ Stretta osservazione e monitoraggio PV
- ✓ Supporto sintomatico : analgesici e/o antipiretici
- ✓ Terapia antibiotica empirica in pz neutropenici --> escludere infezioni
- ✓ Ossigeno, fluidi ev, se necessario uso di vasopressori

TRATTAMENTO DELLA CRS IN CAR T CELL

- ✓ TOCILIZUMAB: - anticorpo monoclonale inibitore dell' IL6
  - nuovo approccio nel trattamento della CRS (FDA), 1° linea
  - dose 8-12 mg/kg (max 800 mg/ dose)
  - ripetibile ogni 8 ore
  - tempo di infusione non meno di un ora
  - appropriata premedicazione

- ✓ STEROIDI - prima e seconda linea nel trattamento della CRS

- ✓ ALTRI AGENTI: Siltuximab, Infliximab, Anakirna, gene suicida



NEUROTOSSICITA’

- E’ un importante e comune complicazione della terapia con i CAR T
- La patogenesi è tuttora sconosciuta
- La disfunzione della barriera emato-encefalica rimane il fattore principale

SINTOMI:

- ❑ Cefalea
- ❑ Vertigini
- ❑ Alterazione stato di memoria (sonnolenza, disorientamento, delirio)
- ❑ Alterazione del linguaggio (disartria, disfagia)
- ❑ Convulsioni
- ❑ Encefalopatia fino a coma

Neurotoxicity assessment

Age <12 years: CAPD

RASS Score ____ (if -4 or -5 do not proceed)

Please answer the following questions based on your interactions with the patient over the course of your shift:

	Never	Rarely	Sometimes	Often	Always	Score
	4	3	2	1	0	
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never	Rarely	Sometimes	Often	Always	
	0	1	2	3	4	
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive—very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					TOTAL	

Figure 1.
Cornell Assessment of Pediatric Delirium revised. RASS = Richmond Agitation and Sedation Scale.

Age ≥12 years

Sign/Symptom	Grade 1	Grade 2	Grade 3	Grade 4
Somnolence[1]	Mild drowsiness / sleepiness	Moderate somnolence, limiting instrumental ADL	Obtundation or stupor	Life-threatening needing urgent intervention or mechanical ventilation
Confusion[1]	Mild disorientation / confusion	Moderate disorientation, limiting instrumental ADL	Severe disorientation, limiting self-care ADL	
Encephalopathy[1]	Mild limiting of ADL	Limiting instrumental ADL	Limiting self-care ADL	
Dysphasia[1]	Dysphasia not impairing ability to communicate	Dysphasia with moderate impairment in ability to communicate spontaneously	Severe receptive or expressive dysphasia, impairing ability to read, write or communicate intelligibly	-
Seizure[1]	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures
Incontinence or motor weakness[1]	-	-	Bowel / bladder incontinence; Weakness limiting self-care ADL, disabling	-
Tremor[1]	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-
Raised intracranial pressure	-	-	Stage 1 or 2 papilledema[2] with CSF OP less than 20 mmHg	Stage 3, 4, or 5 papilledema[2] or CSF OP greater than or equal to 20 mmHg or cerebral edema
Neurological assessment score[3]	Mild (7-9)	Moderate (3-6)	Severe (0-2)	Critical (obtunded; convulsive status epilepticus; motor weakness; papilledema; CSF OP greater than or equal to 20 mmHg; cerebral edema)

CARTOX-10 point assessment scale

- Orientation to year, month, city, hospital, President: **5 points**
- Name 3 objects (point to clock, pen, button): **3 points**
- Ability to write a standard sentence (*e.g.*, National bird is the bald eagle.): **1 point**
- Count backwards from 100 by tens: **1 point**

Traube C. et al. Crit Care Med 2014
Neelapu SS et al. Nat Rev Clin Oncol 2018

Neurotoxicity management

	Grade 1	Grade 2	Grade 3	Grade 4
Management	• Vigilant supervision with aspiration precautions and i.v. hydration • Withhold oral intake of food, medicines, and fluids and assess swallowing • Substitute all oral medications and/or nutrition with i.v. forms if swallowing is impaired • Avoid medications that cause CNS depression • Low doses of lorazepam (0.05 mg/kg (maximum 1 mg per dose) i.v. every 8 hours) or haloperidol (0.05 mg/kg (maximum 1 mg per dose) i.v. every 6 hours) 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 and diagnostic lumbar puncture with measurement of opening pressure; include MRI of the spine if focal peripheral neurological deficits have been observed. CT scan of brain can be performed if brain MRI is not feasible • Perform EEG: if no seizures on EEG, continue prophylactic treatment with levetiracetam (BOX 1); if EEG shows non-convulsive status epilepticus, treat patient according to algorithm A (BOX 4) • Consider anti-IL-6 therapy if CRES is associated with concurrent CRS	• Supportive care and neurological work-up as per grade 1 CRES • Administer anti-IL-6 therapy if associated with concurrent CRS • Dexamethasone 0.5 mg/kg (maximum 10 mg per dose) i.v. every 6 hours or methylprednisolone 1–2 mg/kg per day divided every 6–12 hours for CRES that is not associated with concurrent CRS or is refractory to prior anti-IL-6 therapy • Consider transfer to PICU if associated with grade ≥2 CRS (TABLE 2)	• Supportive care and neurological work-up as per grade 1 CRES • PICU transfer is recommended • Administer anti-IL-6 therapy if associated with concurrent CRS and if not administered previously • Dexamethasone 0.5 mg/kg (maximum 10 mg per dose) i.v. every 6 hours; increase to 20 mg i.v. every 6 hours if patient is refractory to initial doses or methylprednisolone 1–2 mg/kg per day divided every 6–12 hours around the clock if symptoms worsen despite anti-IL-6 therapy or for CRES without concurrent CRS • Continue corticosteroid treatment until improvement to grade 1, and then taper or stop • For patients with stage 1 or 2 papilloedema[b] with a CSF opening pressure <20 mmHg, treat according to algorithm A (BOX 5) • Consider repeat neuro-imaging (CT or MRI) every 2–3 days if ≥3 grade CRES persists	• Supportive care and neurological work-up as per grade 1 CRES • PICU monitoring; consider mechanical ventilation for airway protection • Neurosurgical evaluation • Consider repeating CT scans • Obtain chemistry panels frequently (every 6–8 hours), adjust medication and provide osmotherapy to prevent rebound cerebral oedema, renal failure, hypovolemia and/or hypotension, and electrolyte abnormalities • Anti-IL-6 therapy and repeat neuro-imaging as for grade 3 CRES • Consider high-dose corticosteroids (for example, methylprednisolone 1 g per day i.v. for 3 days followed by rapid taper) • Continue corticosteroids until improvement to grade 1 CRES, and then taper • For patients with convulsive status epilepticus, treat according to algorithm B (BOX 4) • For patients with stage 3, 4, or 5 papilloedema, CSF opening pressure ≥20 mmHg, or cerebral oedema, treat per algorithm B (BOX 5)

Mahadeo KW et al. Nat Rev Clin Oncol

TRATTAMENTO DELLA NEUROTOSSICITA' IN CAR-T

- Monitoraggio continuo dei PV
- ≥ grado 3 di CNS →UTI
- Intubazione e ventilazione meccanica
- Steroidi
- No tocilizumab*

La risoluzione della neurotossicità sembra richiedere più tempo rispetto alla CRS**

*Gust J et al, 2017

** Santomasso BD et al, 2018

SFIDE DEL FUTURO

- ✓ Più di 350 Car T trials registrati nel mondo
- ✓ Più centri specializzati
- ✓ LAM
- ✓ Mieloma
- ✓ Tumori solidi

- ✓ Più training
- ✓ Collaborazione tra i centri di riferimento
- ✓ Più trials e prodotti
- ✓ Monitoraggio degli effetti collaterali a lungo termine
- ✓ Miglioramento dei sistemi produttivi (riduzione dei costi, riduzione dei tempi di produzione, prodotti off-the-shelf)

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