CAR-TALKING

News dal mondo CAR-T

Bari, Hotel Excelsior
22 maggio 2023

CAR-T nel DBCL dalla terza linea
Caso Clinico 2

Elsa Pennese

55 years female

Comorbidities: essential tremor

January 2021:

- night sweats, weight loss (> 10% body weight), fever (T > 38°C)

March 2021:

- Total-body CT scan: **neoformation of mediastinum** (7,5 x 6,6 cm), extended to the **superior and middle pulmonary lobes**, infiltration of the superior vena cava. Formation of 2.4 cm in the liver (secondarism)

- **PET/CT scan:** tissue with colliquate center, involving **middle lobe and part of the right upper lobe**, with associated atelectasis of the right lobe and lymphangitis (SUVmax 27.8), **lymphadenopathy of the anterior mediastinum** (SUVmax 13.5), **in the right paratracheal area** (SUVmax 10.1) **and in the aorto-pulmonary window lymphonodes** (SUVmax 10.8).

Therapy with corticosteroid and heparin, with decrease of symptoms.

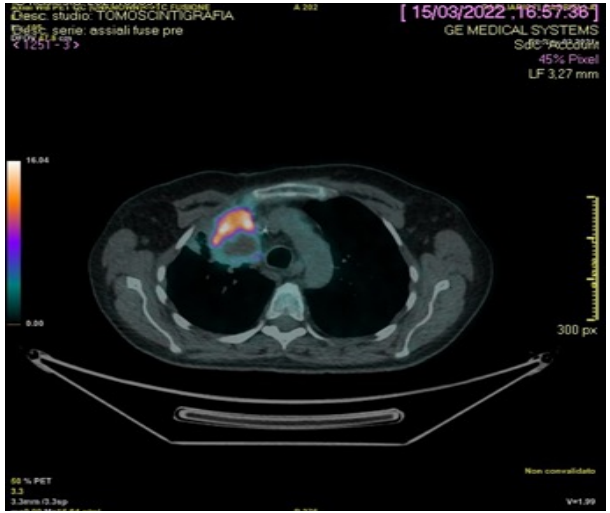
- **Anterior mediastinotomy**:

Diffuse, large-cell, peripheral B-cell-derived lymphoma. CD20+, BCL6+, MUM1+, cMYC+ (50%), BCL2 +, CD30 -/+, CD23 --/+, CD10-. Ki67 80%.

It is not possible to exclude a primary mediastinal B-cell lymphoma.

FISH for c-MYC: negative

DLBCL NOS, CS IV B (L+), IPI 3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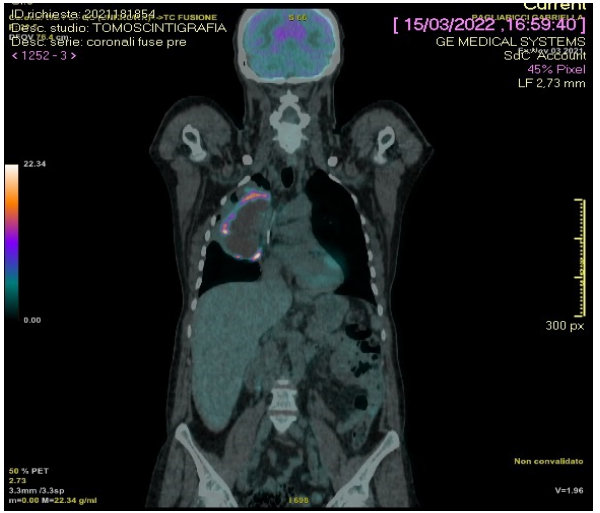
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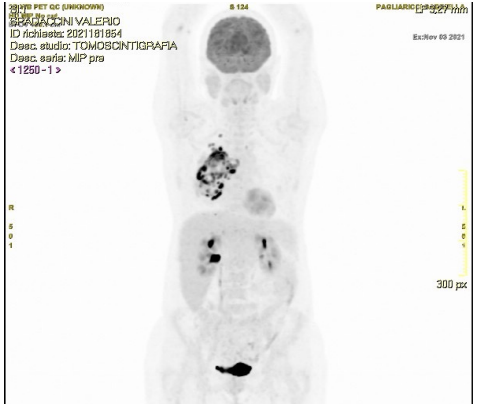
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First line planned treatment: 6xR-COMP-14

Rituximab 375 mg/mq iv d1

Cyclophosphamide 750 mg/mq iv d1

Non Pegylated-Liposomal Doxorubicin 50 mg/mq iv d1

Vincristine 2 mg iv d1

Prednisone 100 mg os d1-5

After 4 cycles of therapy, **new** onset of sweats and fever

- **PET/CT scan after 4 cycles: Refractory Disease (RD)**

Planned salvage treatment: 2 x R-DHAP + autologus peripheral stem cell transplant

Rituximab 375 mg/mq iv, d1

Cisplatin 100 mg/mq iv, d1

Cytarabine 2000 mg/mq iv, two doses, d2

Dexamethasone 40 mg iv, d1-4

- **PET/CT scan after 2 cycles: Refractory Disease (RD)**

Enrollment in CAR-T therapy program

Cosa bisogna valutare in un paziente candidato alla terapia con CAR-T?

Indicazioni cliniche delle CAR-T

(RCP delle CAR-T commerciali: Tisa-cel ed Axi-cel)

- **Tisa-cel** → trattamento di **pazienti adulti** con **DLBCL**
- **Axi-cel** → trattamento di **pazienti adulti** con **DLBCL** e **PMBCL**
- Refrattari o recidivanti, **dopo due o più linee di terapia sistemica**

Criteri di rimborsabilità AIFA

(scheda di monitoraggio)

- **Caratteristiche del paziente** (età, PS, aspettativa di vita)
- **Precedenti terapie effettuate**
- **Comorbidità**
- **Funzione d'organo**

https://www.aifa.gov.it/documents/20142/936093/Scheda+Registro+Kymriah_DLBCL.zip/0568aabd-548f-3f25-61b5-2bfd6c92544f?version=1.0

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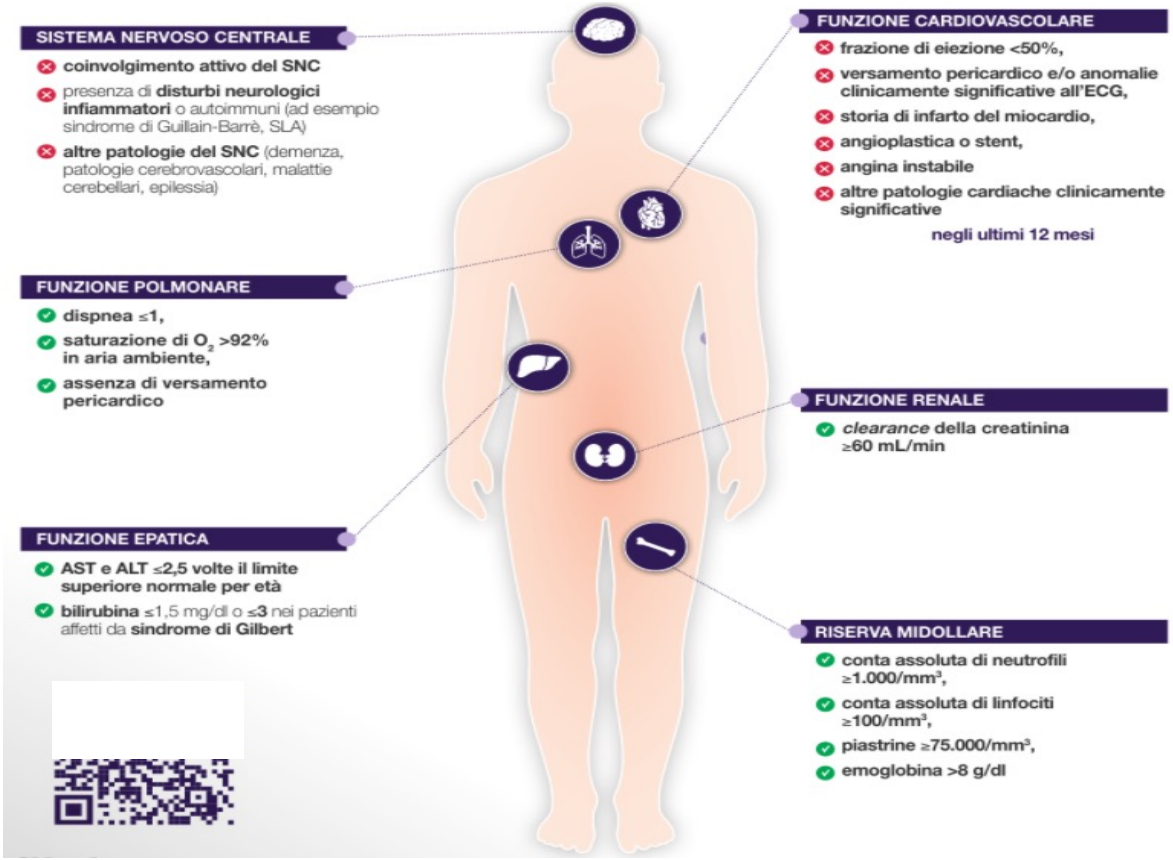
I criteri di rimborsabilità AIFA alla terapia con CAR-T: funzione d'organo



October 2021

Leukapheresis

CAR-T product: Axicabtagene ciloleucel

Bridging therapy: R-IEV

Rituximab 375 mg/mq iv, d1

Ifosfamide 2500 mg/mq iv, d 2-4

Epirubicin 100 mg/mq iv, d2

Etoposide 150 mg/mq iv d 2-4

- **PET/CT scan: Refractory Disease (RD)**

pre-CAR-T screening

- CNS MRI: negative
- EEG: negative
- Echocardiography: normal, EF 65%
- Abdomen ultrasound: hepatic angiomas
- Spirometry: slight reduction of alveolar-capillary diffusion
- Total-body CT scan: solid tissue localized in the right hilo-parail area and reduction in the caliber of the bronchus (with atelectasis of lung parenchyma). Adenopathies in right mediastinal and hilar area (max 25 mm)

1° Hospitalization for CAR-T therapy (40 days from apheresis)
Fever (38°C), cough
Blood cultures: negative
Microbiological monitoring: negative
PCT: 0.07 and RCP 60

Conditioning therapy:
- Cyclophosphamide 500 mg/mq iv d -5 -> -3
- Fludarabine 30 mg/mq iv d d -5 -> -3

d -1 Fever (39.5 C°)
Chest CT scan: right upper lobe pneumonia
Blood cultures: negative
Microbiological monitoring: negative
PCT: 0.14 and RCP 266
Bronchoscopy+BAL: no evidence of infections

2° Hospitalization for CAR-T therapy (70 days from apheresis)

Conditioning therapy:

- Cyclophosphamide 500 mg/mq iv d -5 -> -3
- Fludarabine 30 mg/mq iv d -5 -> -3

CAR-T infusion: 2.0 x 10^6 anti-CD19 CAR T cells/kg

Complications after CAR-T infusion

Cytokine Release Syndrome (CRS)

- Day 2, Grade 2 (hypotension, fever) → **ALERT ICU**

CRS treatment: fluid intake, O2, vasopressor, 1° dose of tocilizumab (8 mg/kg)

- Day 3, Grade max 3

Trasfer to ICU: 2° dose of tocilizumab, dexamethasone 10 mg*4/die

Immune effector cell-associated neurotoxicity syndrome (ICANS)

- Day 6 (tremor, confusion)
- Day 7, Grade max 4

ICANS treatment: methylprednisolone 1 gr/die, Anakinra (100 mg daily for 7 days)

Atrial fibrillation

- Day 8 pharmacologic conversion with amiodarone
- **Day 27 Discharge**

Follow-up

- **PET/CT scan after CAR-T (1 month):** reduction of metabolic data in the right hemithorax (SUVmax 4.9 v 13.5) and in the upper paratracheal (SUVmax 4.0 vs 6.0). Reduction of the metabolic data also in correspondence with adenopathies in the precarenal (SUVmax 2.5) and retrosternal site. Conclusion: **good response to treatment.**

CAR-T circulating cells: 36,9%

day 42: productive cough and fever (39 ° C)

- **Chest CT scan**: **extensive parenchymal consolidation involving a large part of the right lower lobe.** Parenchymal **consolidation in the left upper lobe**. Right pleural effusion.

Follow-up

Bronchospcopy+BAL: presence of fibrinous material with associated fungal hyphae implants that completely occlude the right principal bronchus

BAL culture test: positivity to Aspergillus fumigatus

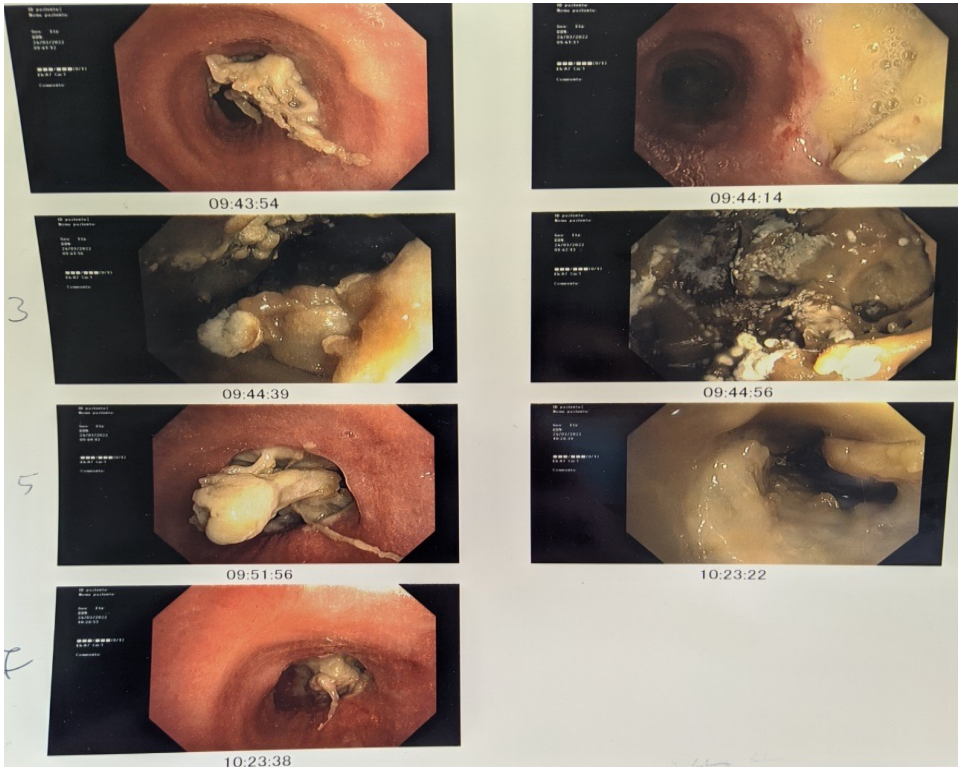
Start therapy with **Amphotericin B 3.0 mg/kg/die**

Follow-up

day 64: persistence of productive cough and high fever (T 39 ° C)

Bronchoscopy: fluctuating hyphae
are observed in right bronchus. The main bronchi on the right side has fungal implants.
The bronchial anatomy is no longer evident due to the presence of a large fungal cave.

High level of CAR-T cells in broncholavage fluid



Follow-up

March 22
Padua Hospital, thoracic surgery and lung transplant center

Tracheal sleeve pneumonectomy: removal of the right lung and necrotic-colliquative material. Left main bronchus anastomosis with trachea and reconstruction of the pericardium using bovine pericardium. Temporary tracheostomy placement

The histological examination was positive for **Veillonella Parvula** and **Aspergillus Fumigatus**

Follow-up

Bronchoscopy: trachea and left hemisystem are normal. Removal of the tracheostomy

PET/CT scan (6 month): Metabolic Complete Remission (MCR)

PET/CT scan (9 month): Metabolic Complete Remission (MCR)

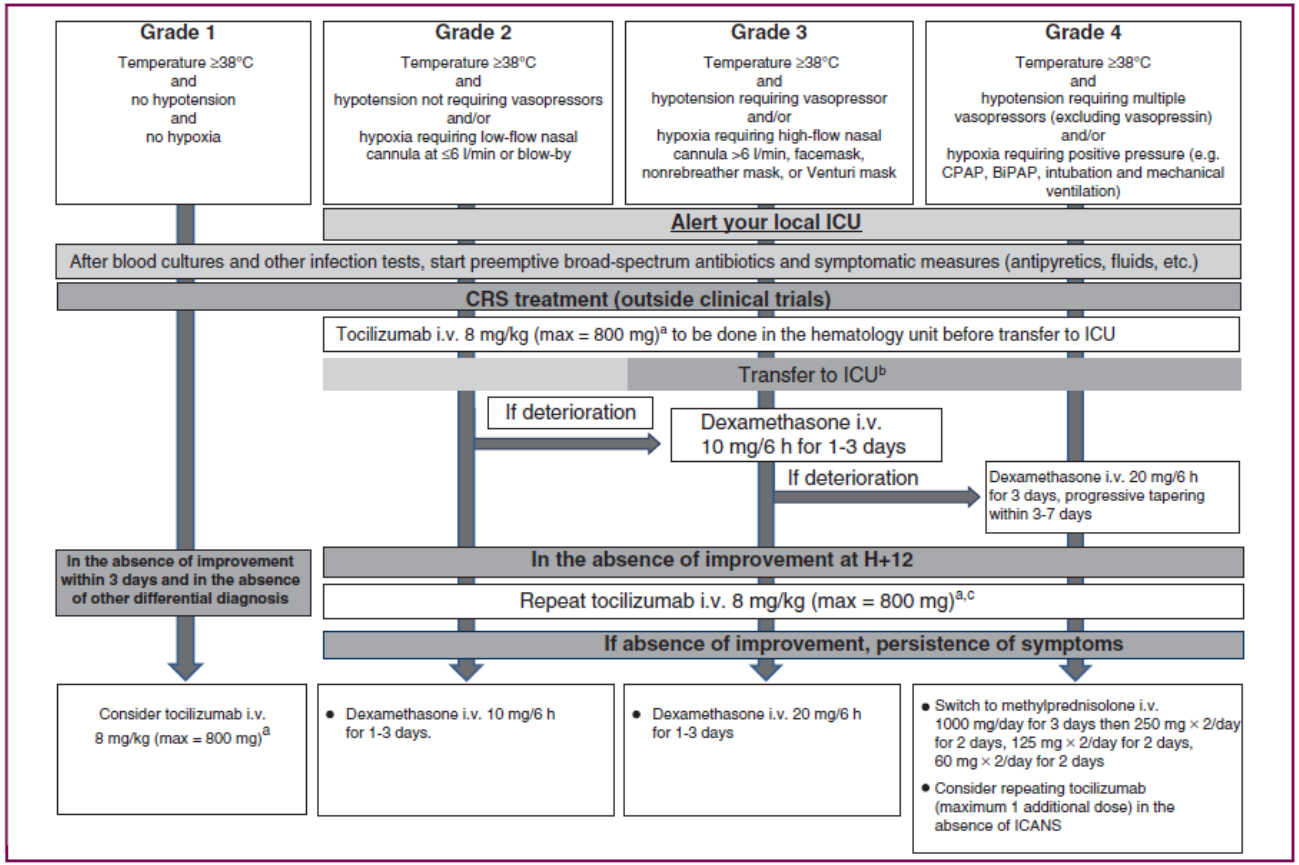
PET/CT scan (15 month): Metabolic Complete Remission (MCR)

SHORT TERM COMPLICATIONS: ADMISSION TO DAY +28

Cytokine release syndrome (CRS)

- CRS affects 30-100% of all patients, with grade ≥ 3 CSR reported in 10-30%
- Incidence depends on the CAR-T product, disease characteristics, CRS grading system used
- Typical onset is between 1 and 14 days post-CAR-T infusion, its duration is commonly between 1 and 10 days.
- Fever (≥ 38°C), hemodynamic instability and hypoxiemia
- Risk factors for high grade CRS: tumor burden, concurrent infections, CAR-T dose and product and LD conditioning intensity.
- CRS markers: hyperferritinemia, C-reactive protein (CRP), IL-6

Grading and management of CRS



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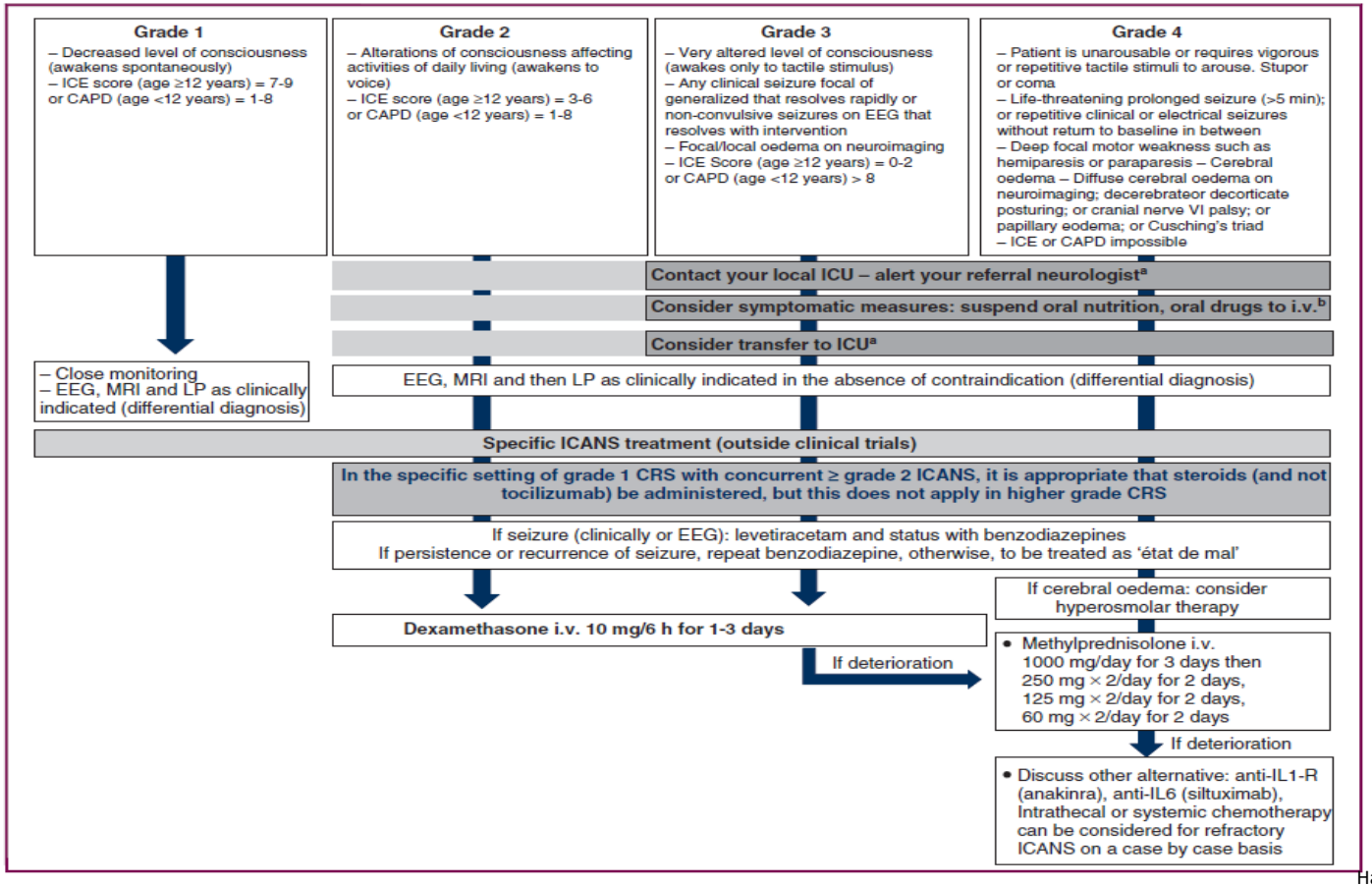
SHORT TERM COMPLICATIONS: ADMISSION TO DAY +28

Immune effector cell-associated neurotoxicities syndrome (ICANS)

- ICANS affects 20-60% of all patients, with grade ≥ 3 ICANS in 12-30%
- Typical onset 3-5 days post-CAR-T infusion, its duration is commonly between 1 and 10 days.
- Symptoms include tremor, confusion, agitation and seizures. Dysphasia, hesitant speech and deterioration in handwriting are prominet and can progress to aphasia.
- Risk factors for high grade ICANS: high disease burden, higher CAR-T doses, pre-existing neurological conditions, low platelet count and early sever CRS

Grading and management of ICANS



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SHORT TERM COMPLICATIONS: ADMISSION TO DAY +28

CARDIOVASCULAR TOXICITIES

- CT affects 10-20% of all patients
- Hypotension requiring vasopressor support was the main cardiac complication; **arrythmias**, miocardial impairment, left ventricular systolic dysfunction, cardiac failure and cardiovascular death are also reported.
- Risk factors for CAR-T CT: grade $\geq$ 2 CRS, high disease burden and pre-existintg cardiac dysfunction following prior exposure to cardiotoxins (anthracyclines, RT and BTK)
- CT is early, largely reversible phenomenon, with rare LVSD beyond 6 months and no late cardiovascular effect at 1 year.

MEDIUM-TERM COMPLICATIONS: DAY +28 TO DAY +100

INFECTIONS AND ANTIMICROBIAL PROPHYLAXIS

- Opportunistic infections are common and prophylaxis is warranted untill immune reconstitution
- Risk factors: bridging therapy and steroids/tocilizumab use for CRS/ICANS, prolonged neutropenia, CD4 T-cell lymphopenia, B-cell aplasia/hypogammaglobulinemia, prior auto/allo-HCT
- First 30 days: bacterial or respiratory viral infections. Invasive fungal infections are rare.
- Beyond day 30: viral infections predominate.

Infection prophylaxis post CAR-T

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS Can consider starting earlier, e.g. day 5,[a] if patient is at high risk of infection, e.g. ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9$/l) following day +28, consider G-CSF	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended[b]	Can be considered in case of prolonged neutropenia and should be based on local guidelines, e.g. with levofloxacin or ciprofloxacin
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800 mg bid	Start from LD conditioning until 1-year post-CAR T-cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1-year post-CAR-T cell infusion AND until $CD4^+$count $>0.2 \times 10^9$/l Where there is prolonged myelosuppression, postpone start after ANC $>0.5 \times 10^9$/l	Can be started later depending on centre guidelines In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300 mg/day) or fluconazole (200 mg/day) or micafungin (50 mg i.v./day) in patients with severe (ANC $<0.5 \times 10^9$/l) or prolonged (>14 days) neutropenia and/or in patients on long-term or high-dose (>72 h) corticosteroids or in patients post-allo-HCT	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
i.v. Immunoglobulin	Routine in children. Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	Clinical evidence does not support routine use in adults following allo-HCT

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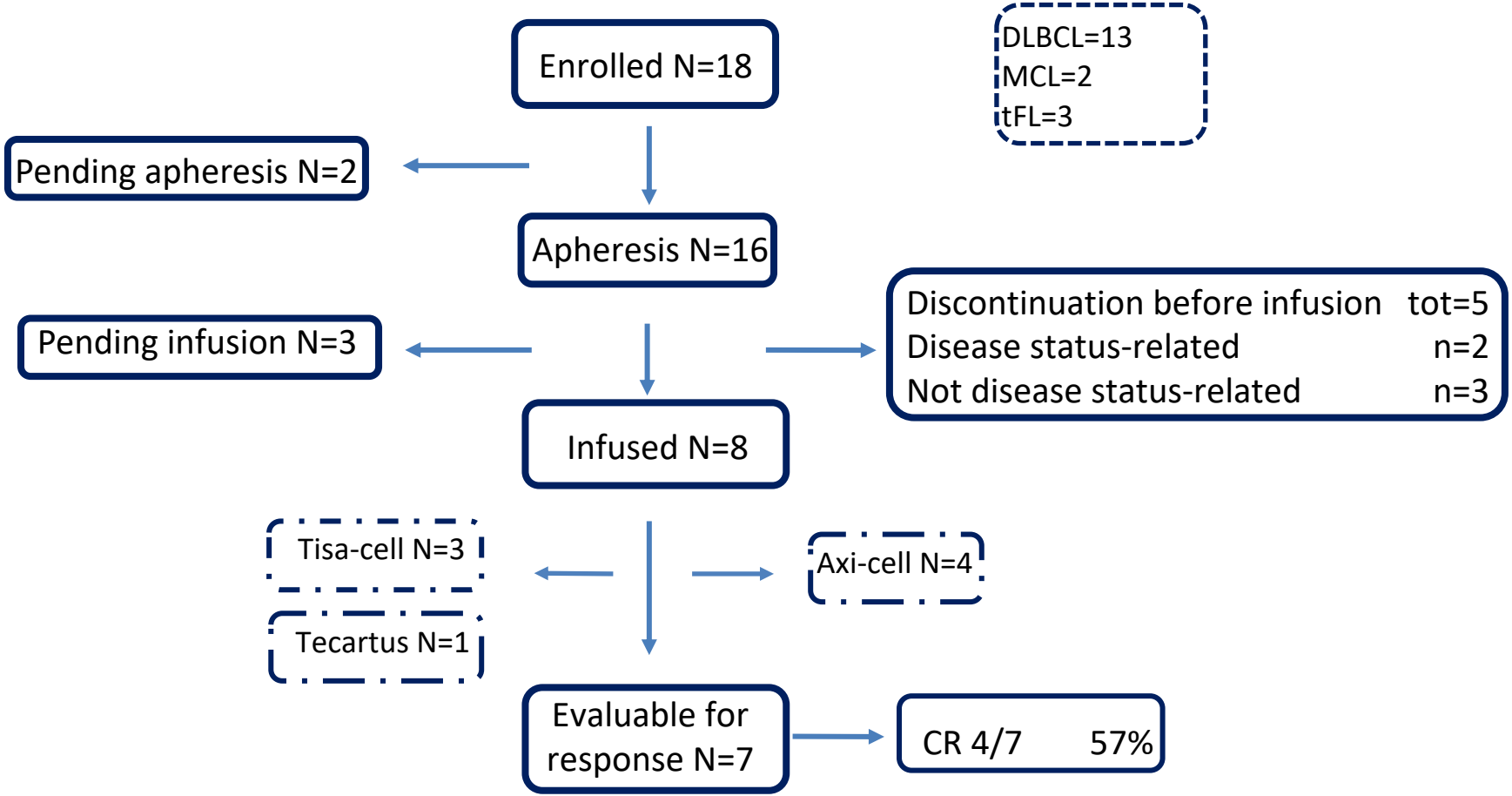
Terapia con CAR-T: esperienza del Centro di Pescara: Marzo 2021-Maggio 2023



Conclusions

- CAR T-cell therapies have **undoubtedly** revolutionized the treatment of R/R LBCL
- CAR T-cell therapies represent a valuable new treatment option, yelding **impressive** CR rates and **improving** OS
- CAR T-cell therapy confers a risk of potentially life –threating toxicities
- Comphrensive training of personel involved in CAR-T delivery, including intensive care unit (ICU) and neurology specialist, is key.

Conclusions

The optimal management of infectious complications remains a clinical question

It is not currently known whether certain subgroups of CAR T-cell recipients may benefit from anti-mould prophylaxis.
Guidelines suggest posaconazole, fluconazole or micafungin prophylaxis during neutropenia is a good approach.

Further controlled studies in the CAR T-cell therapy are required to better defined post-infusion risk factors for serious infections

Large multicenter prospective studies are necessary to establish best practice for prevention and management Invasive Fungal Infections (IFIs) in this vulnerable population.

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Grazie per l'attenzione..