CAR-Team

CASO CLINICO

Gestione delle tossicità acute che insorgono dopo trattamento con CAR-T

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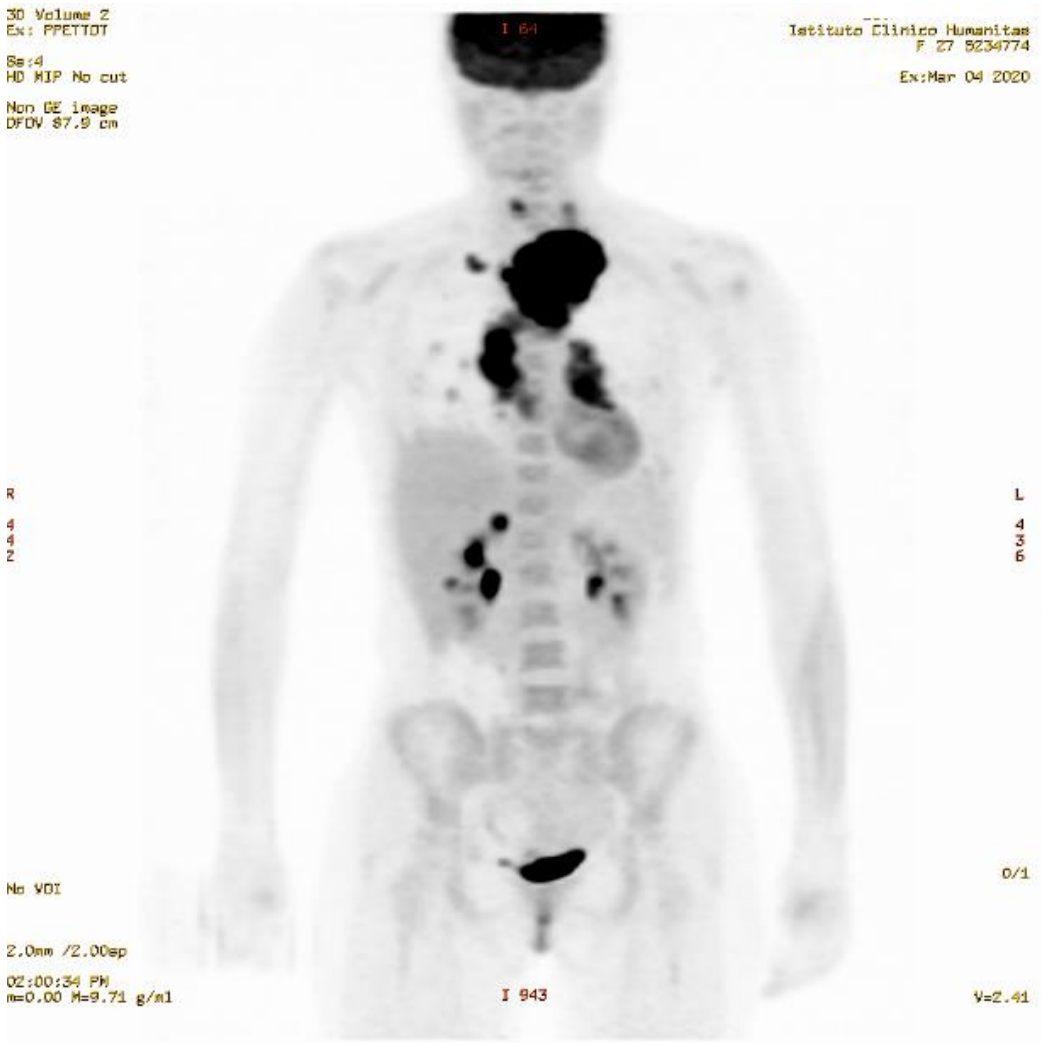
Medical history

Female, 29 years

- 04/2019: **PMBCL stage IIXB, R-IPI 1 (LDH), NCCN-IPI 1**
- 05/2019–11/2019: **R-CHOP x 6 + 2 rituximab**
- 12/2019: **PD**
- 01/2020–02/2020: **R-DHAP x 2**
- 03/2020: **PD**

- **13/03/2020:** lymphocyte apheresis
- Bridging therapy: mediastinal RT (30Gy in 15fz)
- **23/04/2020:** starting lymphodepleting therapy (Flu-Cy)
- fludarabin 30 mg/m^2 and cyclophosphamide 500 mg/m^2

dates agreed with cell lab + ICU !!!



Day 0

28/04/2020 CAR-T infusion

- WBC 1.2 x10^9/L, PCR 0.8 mg/dL
- Renal and liver blood tests: Normal
- No active infections
- PA 110/70
- FC 80
- SpO_2 99%

- ✓ ***Patient's identity check***
- ✓ ***Thawing***
- ✓ ***Y-connector***
- ✓ ***Normal saline solution to rinse tubing and bag***
- ✓ ***Monitoring***

Clinical monitoring for CRS and ICANS

- Vital signs monitoring every 4 hours
- Execution of laboratory blood tests daily:
  - ✓ C-reactive protein (CRP), ferritin, interleukin(IL)-6
  - ✓ Complete blood count (CBC), comprehensive metabolic panel (CMP), coagulopathy
- Daily neurological assessment
- ICE score evaluation every 8 hours

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome

Day +2

- FEVER 38.2°C
- PA 110/70
- FC 80
- SpO_2 99%

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

Daniel W. Lee et all

ASTCT CRS consensus grading

ASBMT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°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‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

ASTCT: American Society for Transplantation and Cellular Therapy ASBMT: American Society for Blood and Marrow Transplantation; BiPAP: bilevel positive airway pressure; CPAP: continuous positive airway pressure; CTCAE: Common Terminology Criteria for Adverse Events

Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

Day +2

Fever 38.2°C

CRS grade 1 (according to ASTCT grading)

Blood tests: WBC 0.7 x10^9/L, N 0.5 x10^9/L

Fever 38.2°C

CRS grade 1 (according to ASTCT grading)

Question 1

How would you manage the patient at this time?

A. Control fever with paracetamol/NSAI-D + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support

B. Control fever with tocilizumab + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support

C. Control fever with steroid + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support

D. Transfer to ICU

Fever 38.2°C

CRS grade 1 (according to ASTCT grading)

Correct answer to question 1: A

How would you manage the patient at this time?

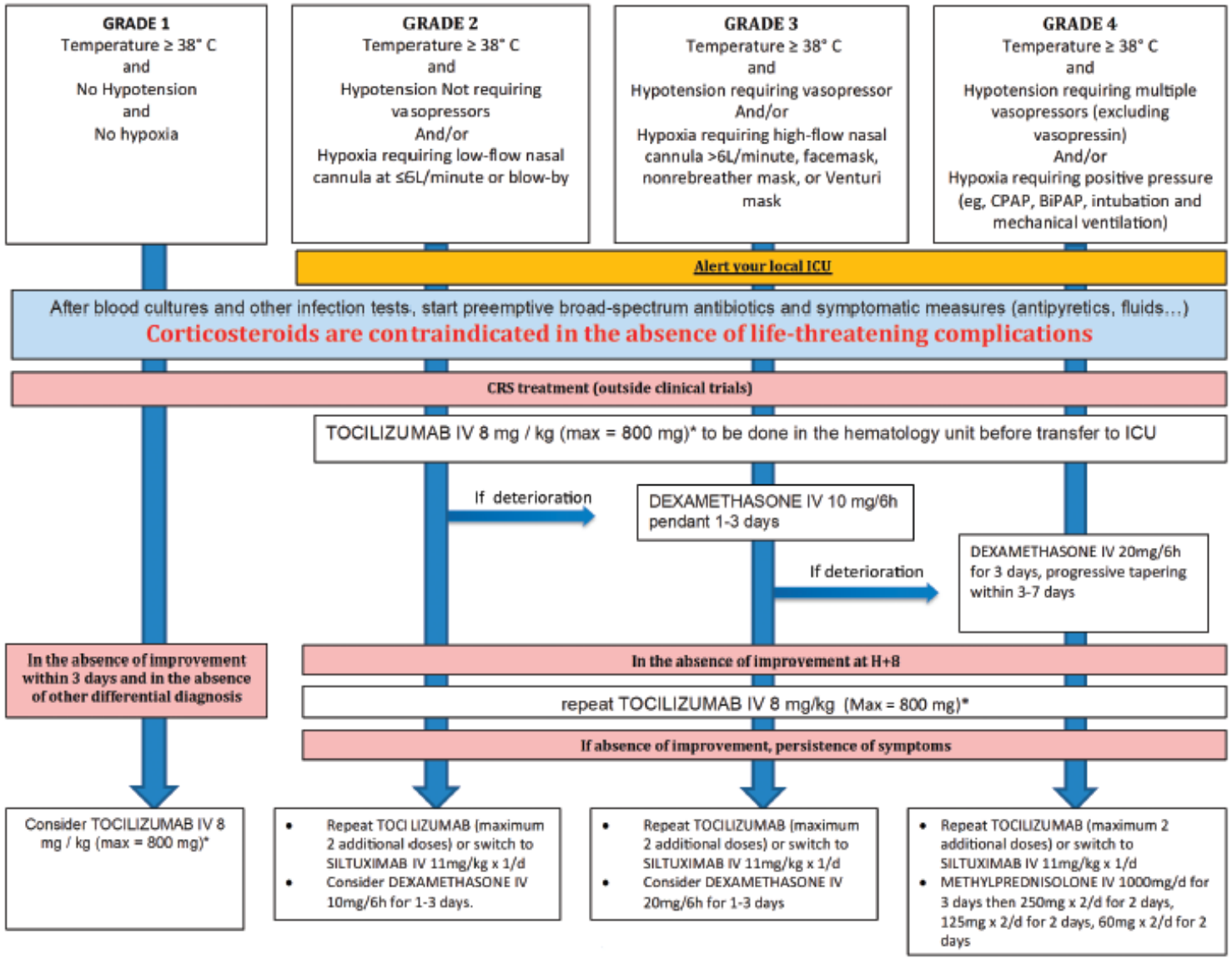
A. **Control fever with paracetamol/NSAI-D + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support**

B. Control fever with tocilizumab + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support

C. Control fever with steroid + rule out infection (blood tests + imaging) + large spectrum antibiotics + transfusional support

D. Transfer to ICU

Management of CRS - EBMT guidel



Yakoub-Agha I, et al. Haematologica 2020; 105: 297–316

Fever 38.2°C

CRS grade 1 (according to ASTCT grading)

Management: Supportive care

- ✓ Control fever with paracetamol/NSAI-D
- ✓ Rule out infection (blood tests + imaging)
- ✓ Large spectrum antibiotics
- ✓ Transfusional support

CRS: Proposed definition (ASTCT consensus)

"Supraphysiologic response following any immune-therapy resulting in activation or engagement of endogenous or infused T cells and/or other immune effector cells.

- Symptoms **can** be progressive
- **Must** include **fever** at the onset
- **May** include hypotension, capillary leak, hypoxia and end organ dysfunction"

Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

Hypotension 80/40

- FEVER 38.3°C
- PA 80/40
- FC 100
- SpO_2 97%

0.9% normal saline bolus of 1L in 1 hour

PA 110/70

ASTCT CRS consensus grading

ASBMT CRS Consensus Grading

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Hypotension 80/40

CRS grade 2 (according to ASTCT grading)

Question 2

How would you manage the patient at this time?

A. Control fever + optimize O_2 support + infuse blood products + infuse methylprednisolone

B. Control fever + optimize O_2 support + infuse blood products

C. Control fever + optimize O_2 support + infuse blood products + infuse tocilizumab

D. Control fever + optimize O_2 support + infuse blood products + infuse dexamethasone

Hypotension 80/40

CRS grade 2 (according to ASTCT grading)

Correct answer to question 2: C

How would you manage the patient at this time?

A. Control fever + optimize O_2 support + infuse blood products + infuse methylprednisolone

B. Control fever + optimize O_2 support + infuse blood products

C. Control fever + optimize O_2 support + infuse blood products + infuse tocilizumab

D. Control fever + optimize O_2 support + infuse blood products + infuse dexamethasone

Hypotension 80/40

CRS grade 2 (according to ASTCT grading)

Management: 0.9% normal saline bolus of 1L in 1 hour

According to ongoing guidelines:

- **tocilizumab** (anti-IL-6 receptor antagonist)

Rational for **earlier use of toci**lizumab without waiting until later stage in the course of CRS:

- available data support that tocilizumab does not affect CAR-T expansion or persistence

Tocilizumab

Vials

- 80 mg/4 mL
- 200 mg/10 mL
- 400 mg/20 mL

Concentration

- 20 mg/mL

Dose

- <30 Kg: 12 mg/Kg
- ≥30 Kg: 8 mg/Kg iv (max 800 mg)

Infusion

- Over 1h
- In a dedicated line

RCP Tocilizumab

Persistence of fever

CRS grade 2 (according to ASTCT grading)

For persistance of fever after 8 hours from the first dose of tocilizumab…

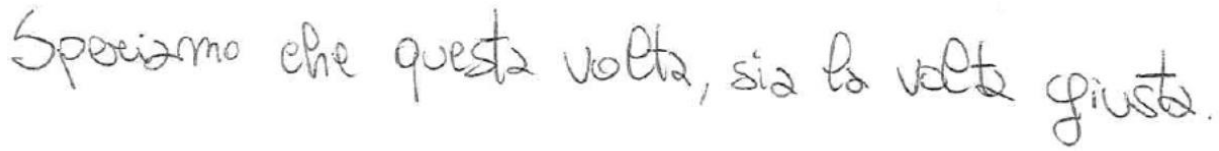
…**OTHER 2 DOSES of tocilizumab** were administered to the patient

Persistence of fever

Neurological impairment

Ideomotor impairment and dysgraphia

- Basal



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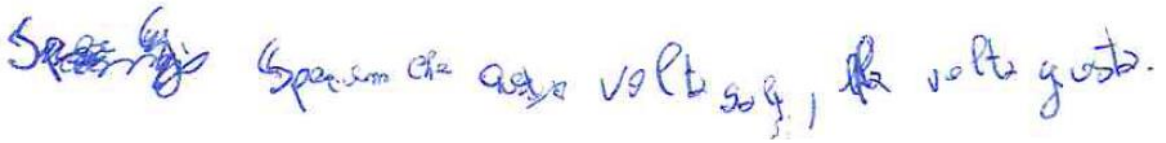

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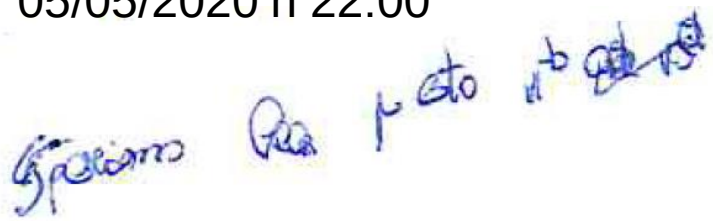


ASTCT grading criteria for ICANS: ICE score

ICE

- **Orientation**: orientation to year, month, city, hospital: 4 points
- **Naming**: ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands**: ability to follow simple commands (eg. «Show me 2 fingers» or «Close your eyes and stick out your tongue»: 1 point
- **Writing**: ability to write a standard sentence (eg. «Our national bird is the bad eagle»): 1 point
- **Attention**: ability to count backwards from 100 by 10: 1 point

Scoring:

- 10, no impairment
- 7–9, grade 1 ICANS
- 3–6, grade 2 ICANS
- 0–2, grade 3 ICANS
- 0, patient unarousable and unable to perform ICE, grade 4 ICANS

Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

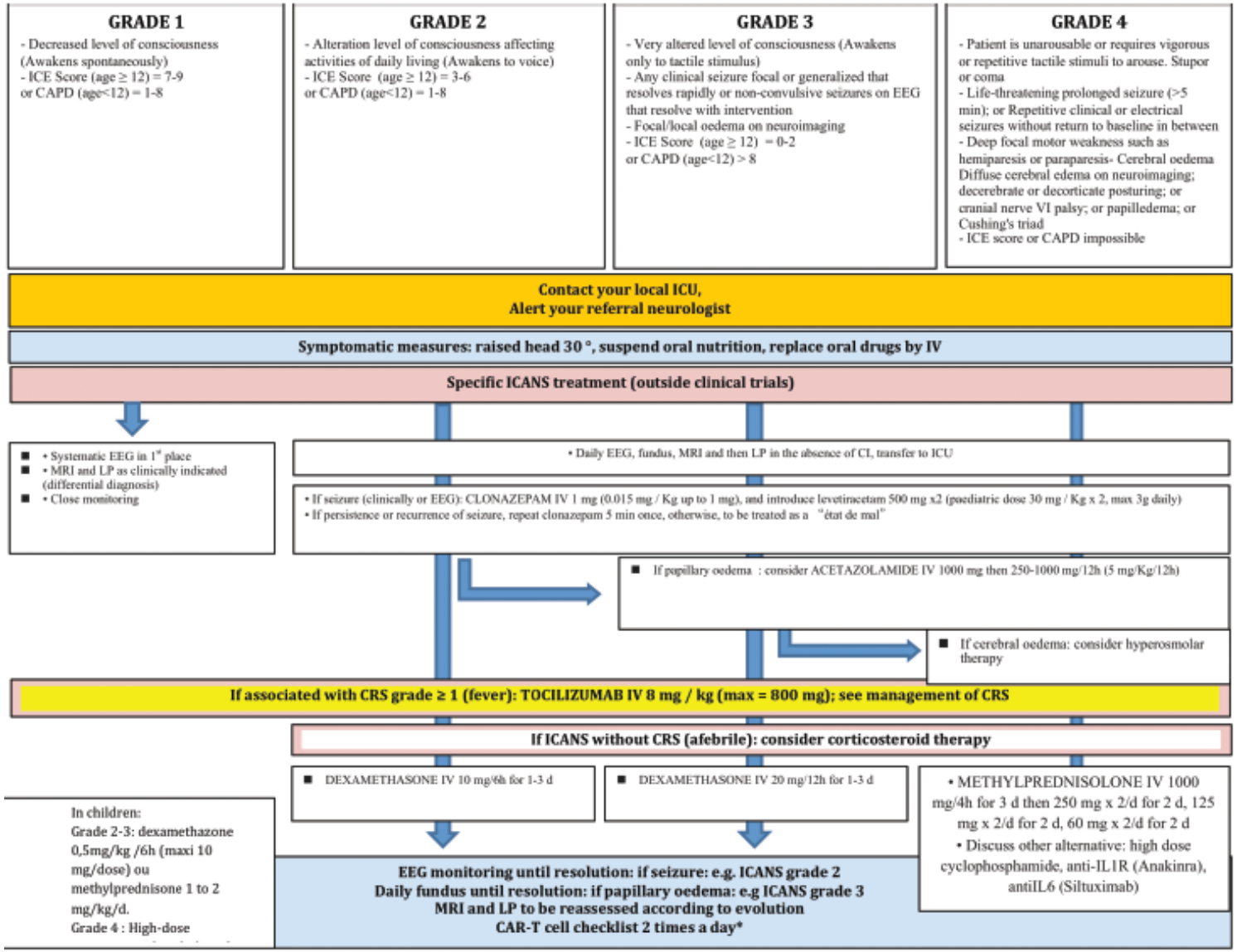
ASTCT grading criteria for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	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§	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS grade 1 (according to ASTCT grading)

Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

Management of ICANS - EBMT guidelines



Yakoub-Agha I, et al. Haematologica 2020; 105: 297–316

Ideomotor impairment + dysgraphia

ICANS grade 1 (according to ASTCT grading

Starting levetiracetam as prophylactic anticonvulsant therapy

Symptomatic measures:

- ✓ Suspend oral nutrition
- ✓ Replace oral drugs by IV

Search for differential diagnosis:

- EEG
- MRI
- Lumbar puncture for diagnosis of bacterial, fungal or viral CNS infection

After few hours

Worsening of symptoms ...

Open eyes only to tactile stimulus-GCS9

No fever

ASTCT grading criteria for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	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
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ICE 0 may be classified as grade 3 ICANS if patient is awake with global aphasia

Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

Hypotension 80/40

ICANS grade 3

Question 3

How would you manage the patient at this time?

A. Symptomatic measures + infuse IV tocilizumab

B. Symptomatic measures + infuse IV tocilizumab + dexamethasone 10 mg x 4/die x 3 days

C. Symptomatic measures + dexamethasone 10 mg x 4/die x 3 days

D. Transfer to ICU

Hypotension 80/40

ICANS grade 3

Correct answers to question 3: C and D

How would you manage the patient at this time?

A. Symptomatic measures + infuse IV tocilizumab

B. Symptomatic measures + infuse IV tocilizumab + dexamethasone 10 mg x 4/die x 3 days

C. Symptomatic measures + dexamethasone 10 mg x 4/die x 3 days

D. Transfer to ICU

Ideomotor impairment + dysgraphia

ICANS grade 3

ICANS grade 3 (according to ASTCT grading)

Starting dexamethasone 10 mg x 4

Transfer to ICU

Day +8

Worsening of symptoms ...

Unarousable coma

ASTCT grading criteria for ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	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
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ICE 0 may be classified as grade 3 ICANS if patient is awake with global aphasia

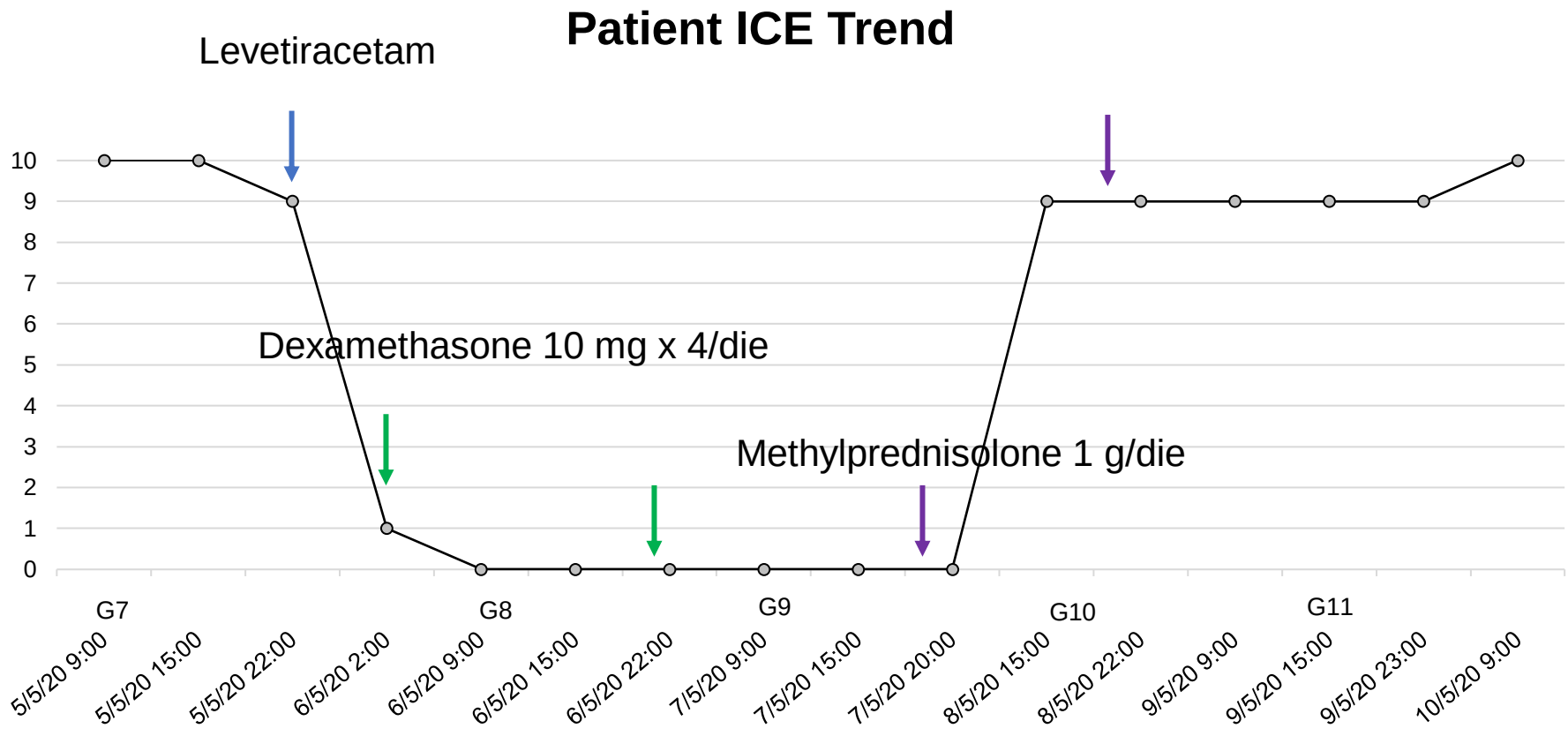
Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625

Unarousable coma

ICANS grade 4 (according to ASTCT grading)

Starting methylprednisolone 1 g/die

ICANS trend

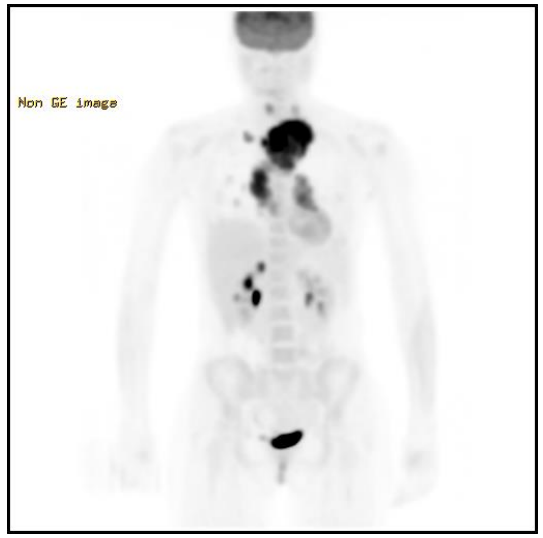


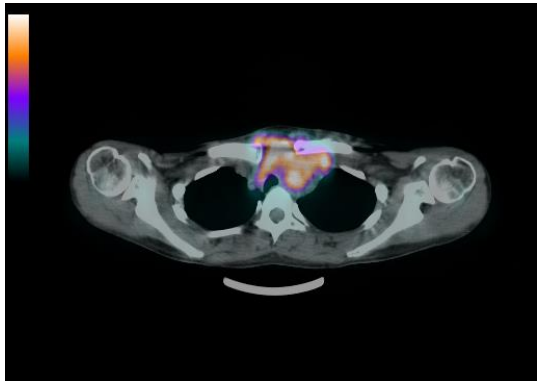
Ideomotor impairment and dysgraphia (ICANS 1) → levetiracetam

Open eye to pression - GCS9 (ICANS 3) → dexamethasone 10 mg x 4

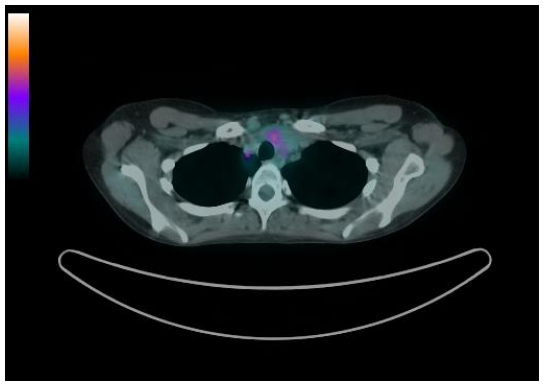
Unarousable coma (ICANS 4)→ methylprednisolone 1 g/die for 2 days and then tapered

ICANS trend

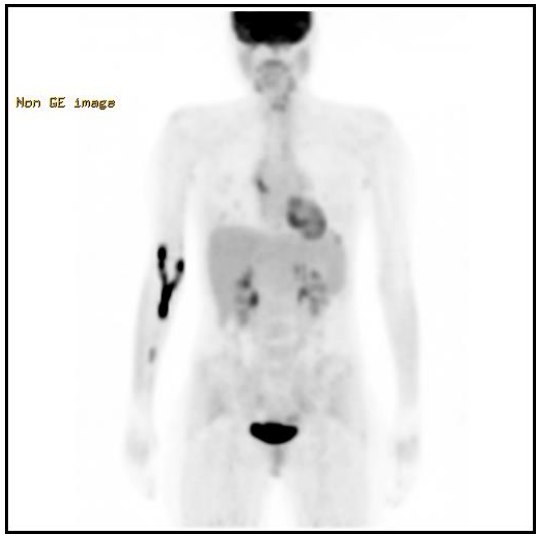


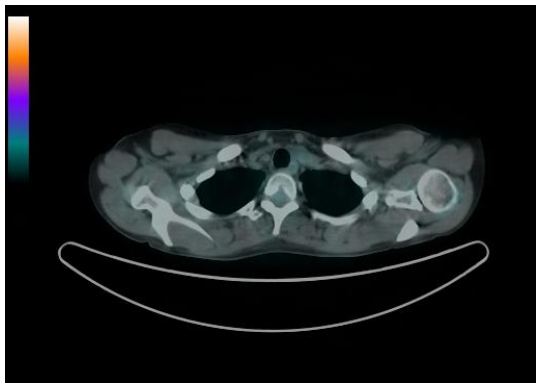


04/03/2020
PD after R-DHAP
DS: 5

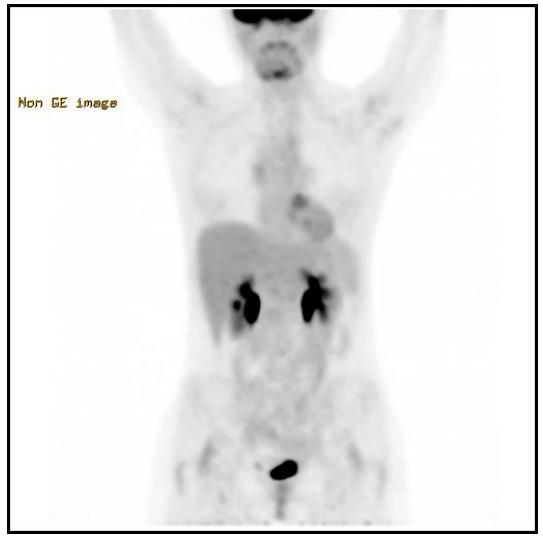


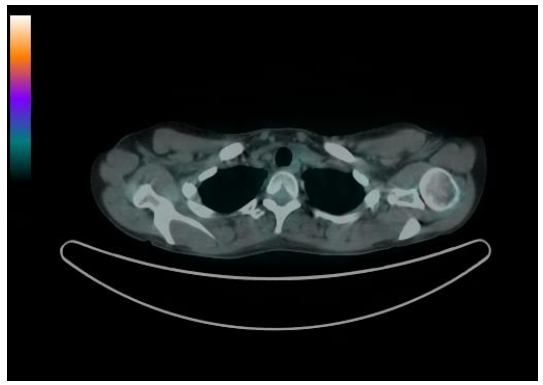
10/04/2020
After mediastinum RT 30Gy
DS: 5
Stable disease





25/05/2020
One month after CAR-T
DS: 4
Partial response





10/10/2020
6 months after CAR-T
DS: 2
Complete response

28/04/20 → CAR-T cell