Expanding Roles of CAR-T Therapy in Hematologic Malignancies

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Objectives

1) To review the basic pathophysiology of human immune response.

2) To understand the function and mechanisms of action of CAR-T therapy.

3) To recognize the significant side effects of CAR-T therapy and how to manage them.

Human Immunology

White blood cells differentiate into two immune pathways to help defend ourselves from harmful pathogens.

- Innate pathway (Nonspecific):
  - Dendritic cells, macrophages, myeloid cells, NK cells phagocytes, mast cells.

- Adaptive pathway (Acquired Immunity):
  - B lymphocytes, T lymphocytes, Antigen presenting cell (APC)

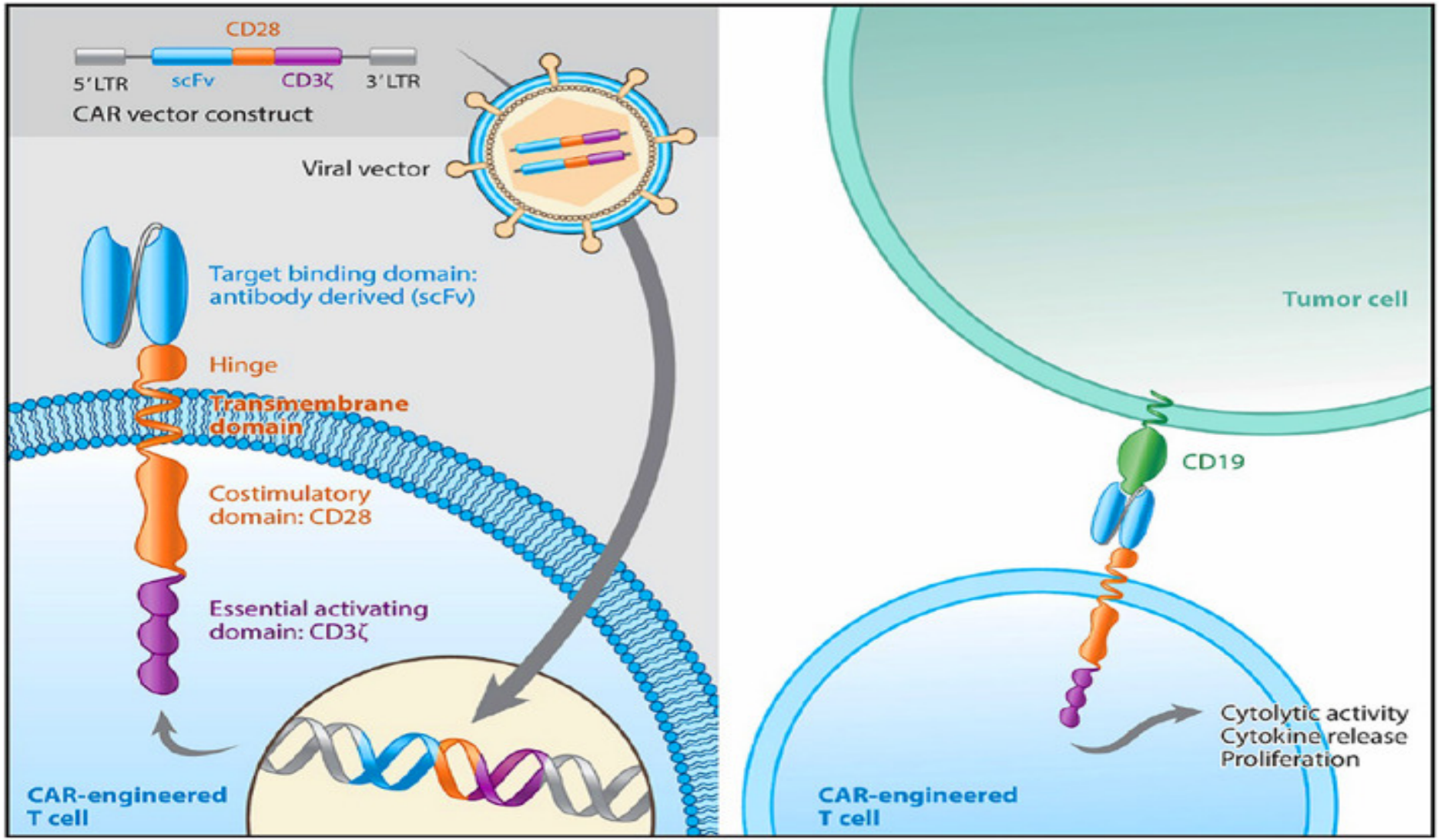
Adaptive Immune Response

- B Lymphocytes (Humoral immunity): Lined with antibodies to recognize and match to specific antigens (memory B and plasma cells release antibodies)
- T Lymphocytes (Cell mediated immunity): Help activate antigens/cytokines to trigger immune response.
- Helper T cells (CD+4) recognize antigens expressing MHC class II.
- Cytotoxic T Cells (CD+8) recognize antigens expressing MHC (major histocompatibility complex created by APC) class I.
- Each T cell has a co-stimulatory receptor that binds to specific B receptor in a tumor cell causing destruction of specific targeted cell.

Chimeric Antigen Receptor

- CAR stands for **Chimeric Antigen Receptor**.
- CAR is a genetically engineered, special receptor that is created in a laboratory to target specific tumor antigen
- The gene blueprint is placed in an inactive viral vector and inserted in the T-cell. A CAR-T cell is created that will then find and kill specific cancer cells.

Making of a CAR-T cell



(1) I. Papadouli, et al. 2020

Chimeric Antigen Receptor

Chimeric Antigen Receptor (CAR)

Extracellular domain:

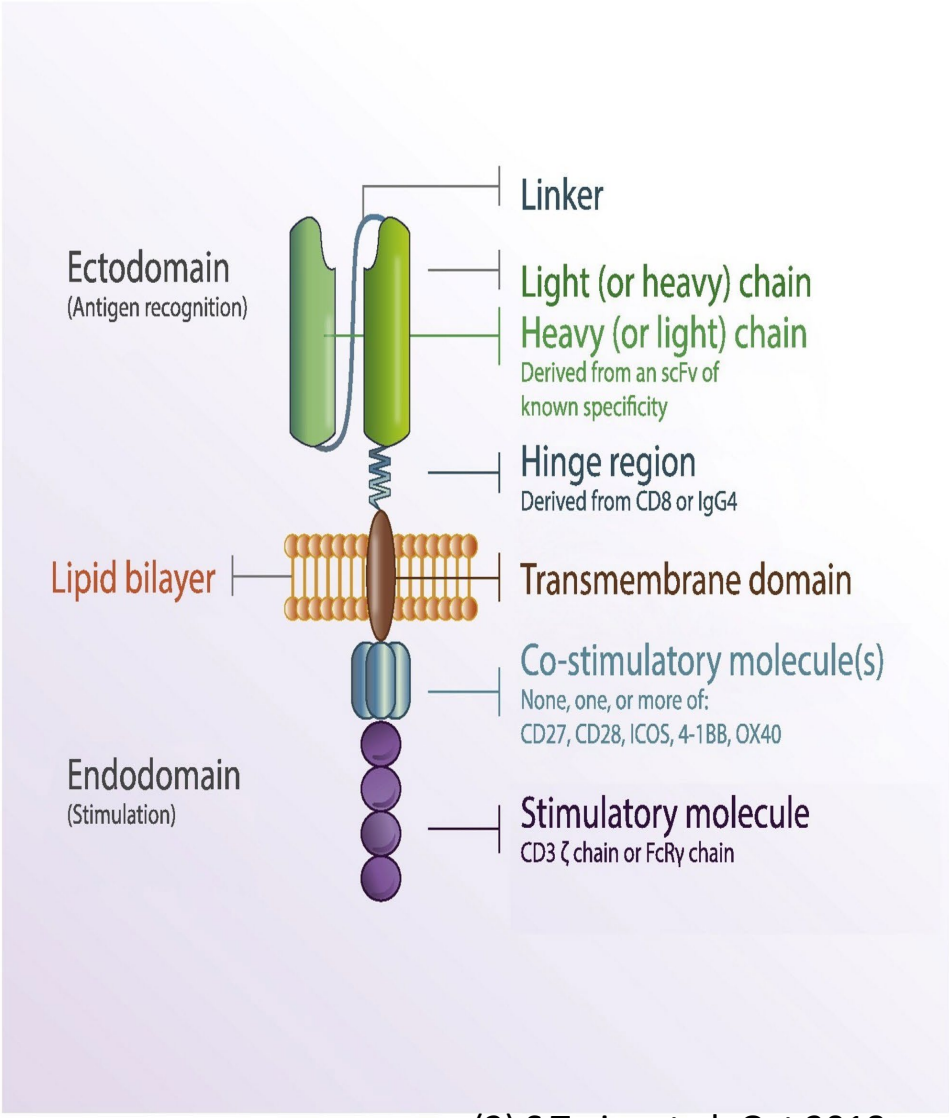
- Redirects T-cell function and connects to antigens

Transmembrane domain:

- Connects Extra/Intra Cellular regions

Intracellular domain:

- Contains co-stimulatory molecules that transmit activation signals once they bind to an antigen



(2) S.Tariq, et al; Oct 2018

Indications/products for CAR-T Therapy

FDA approved indications for CAR-T therapy

1) Lymphomas: DLBC, Follicular, Mantle Cell & Primary Mediastinal
2) Multiple Myeloma
3) Acute Lymphoblastic Leukemia

CAR-T products available:

1) Brexucabtagene Autoleucel (Tecartus): mantle cell, B-cell ALL
2) Axicabtagen ciloleucel (Yescarta): DLBC and Follicular lymphoma
3) Ciltacabtage autoleucel (Carvykti): multiple myeloma
4) Lisocabtagegn Maraleucel (Breyanzi): large B cell lymphoma
5) Idecabtagene Vicleucel (Abecma): multiple myeloma
6) Tisagenlecleucel (Kymriah): Follicular and DLBC. B-cell ALL (peds)

CAR-T Clinical Trials

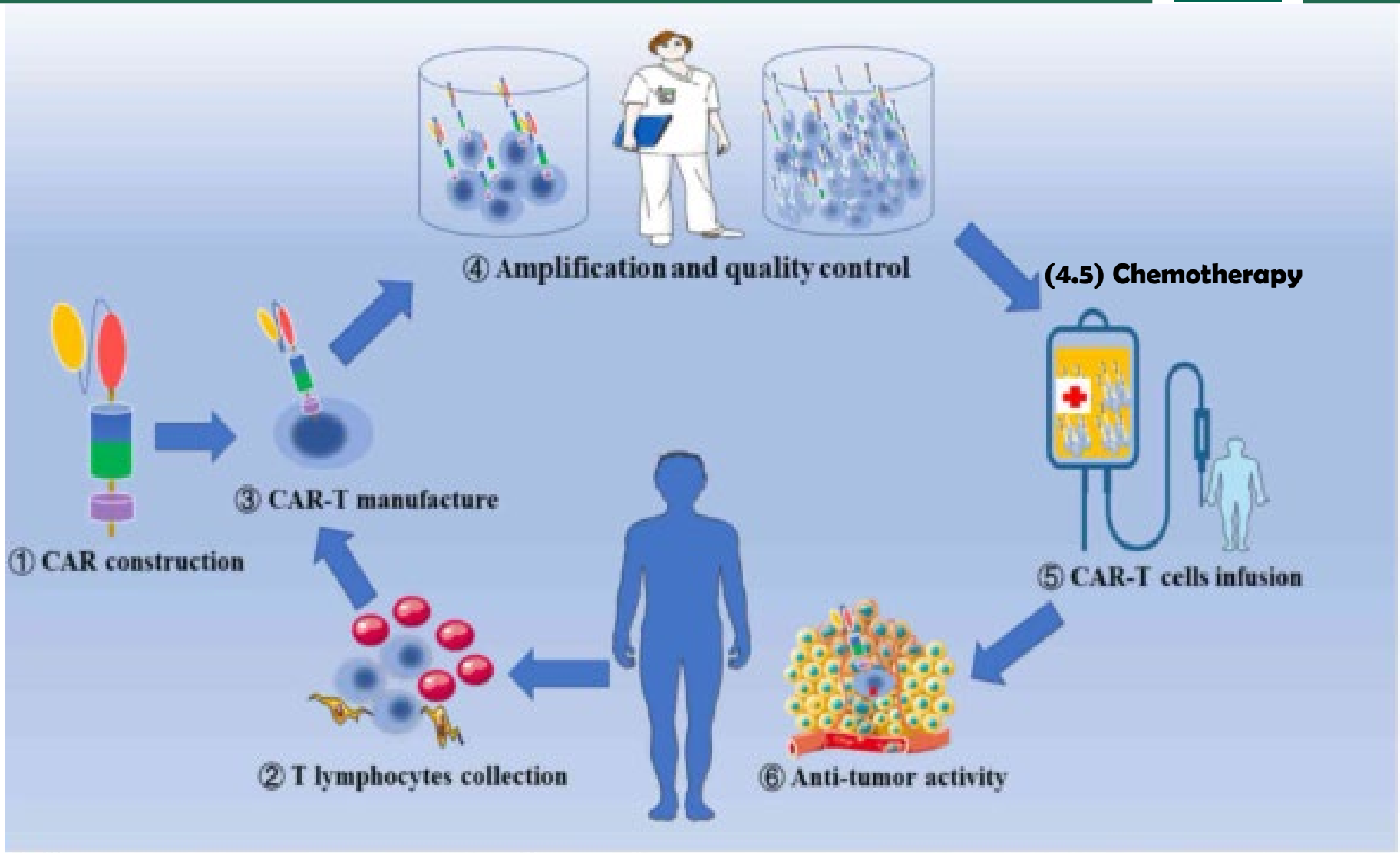
ZUMA-1 trial:

- Refractory Large B cell Lymphoma: Axicabtagen ciloleucel (Yescarta) CAR-T with CD19 Target
- Primary endpoint with 82% ORR and 54% CR. Overall survival rate at 18 months was 52% (3)

ZUMA-2 trial:

- Mantle Cell Lymphoma: Brexucabtagene Autoleucel (Tecartus) CAR-T with CD19 target
- 12 month PFS of 61% with overall survival rate of 83%. (4)

CAR-T Collection and Infusion



(5) B. Long et al, 2020)

CAR-T side effects and management

Potential Side Effects

There are several potentially life-threatening toxicities to monitor for post CAR-T treatment:

1. Cytokine Release Syndrome (CRS)
2. Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
3. Macrophage Activation Syndrome
4. Tumor Lysis Syndrome
5. B-Cell Aplasia

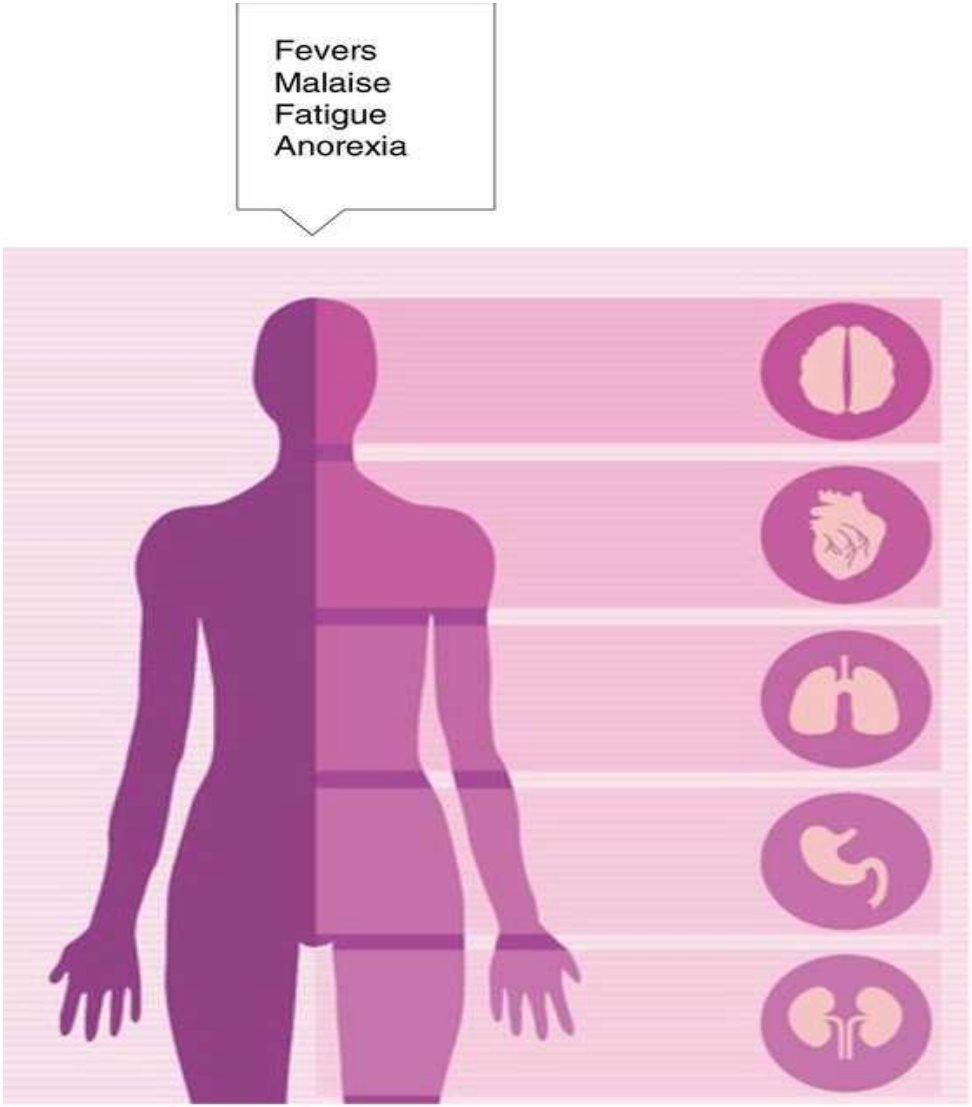
Cytokine Release Syndrome

- **Cytokine Release Syndrome (CRS)** is the result of CAR-T binding to the specific tumor cell, triggering an inflammatory cascade resulting in the release of macrophages which then activate release of IL2 & IL6.

- Cell damage caused by this process leads to capillary damage, vascular leakage into multiple tissues and CSF infiltration with inflammatory cytokines.

- This process can occur between day 1 to day 7 after infusion (depending on CAR-T product used and disease treated) but can also occur later.

Cytokine Release Syndrome



(6) A. Roche; Med Intensiva. 2019;43:480–8

CRS Grading (Lee Grading)

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.

(7) D. Lee, et al; 2014

CRS Management (Lee Criteria)

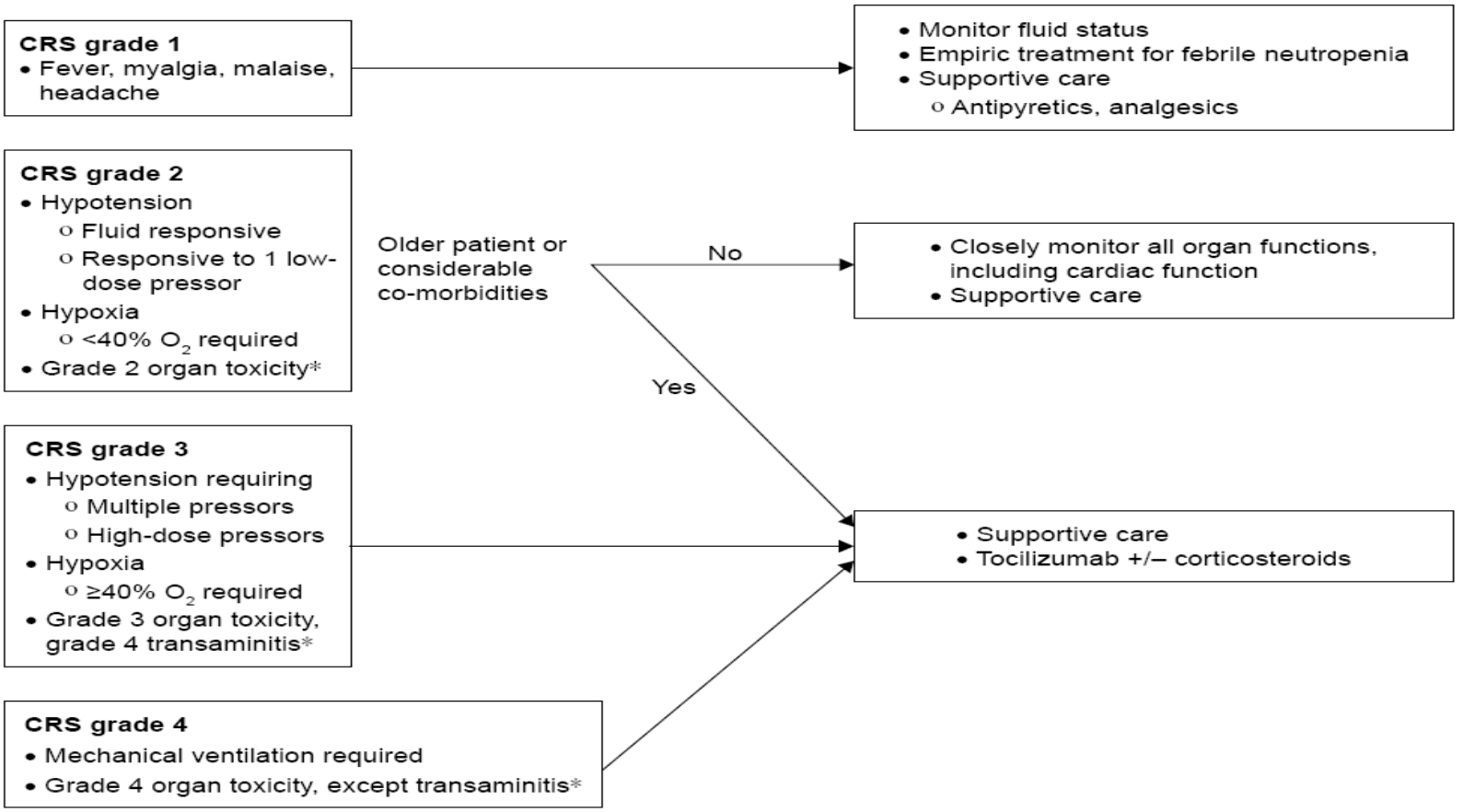


Figure 3 CRS management algorithm by Lee et al.[9]
Notes: The Lee criteria were designed in such a way so that grading can be tied to a management algorithm. Supportive care is the backbone of therapy with anti-cytokine therapy in the form of tocilizumab with or without corticosteroids implemented for grade 3 or higher CRS or for grade 2 in high-risk patients. *Grade of organ toxicities determined by CTCAE v4.03.
Abbreviations: CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

(7) D. Lee, et al; 2014

Treatment of CRS

Tocilizumab (Actemra):

- Anti-IL-6R (monoclonal) antibody binding to IL-6 receptors but does not suppress T-Cell function or affect the CAR-T cells
- Used with Grade 2-4 CRS and patient stability.
- Dose is 8 mg/kg IV (Max 800mg) over 1 hour. Can repeat in 8-12 hours if no improvement.
- Steroids (low dose/high dose Decadron) can be used if CRS unresponsive to Tocilizumab (Grade 3-4)

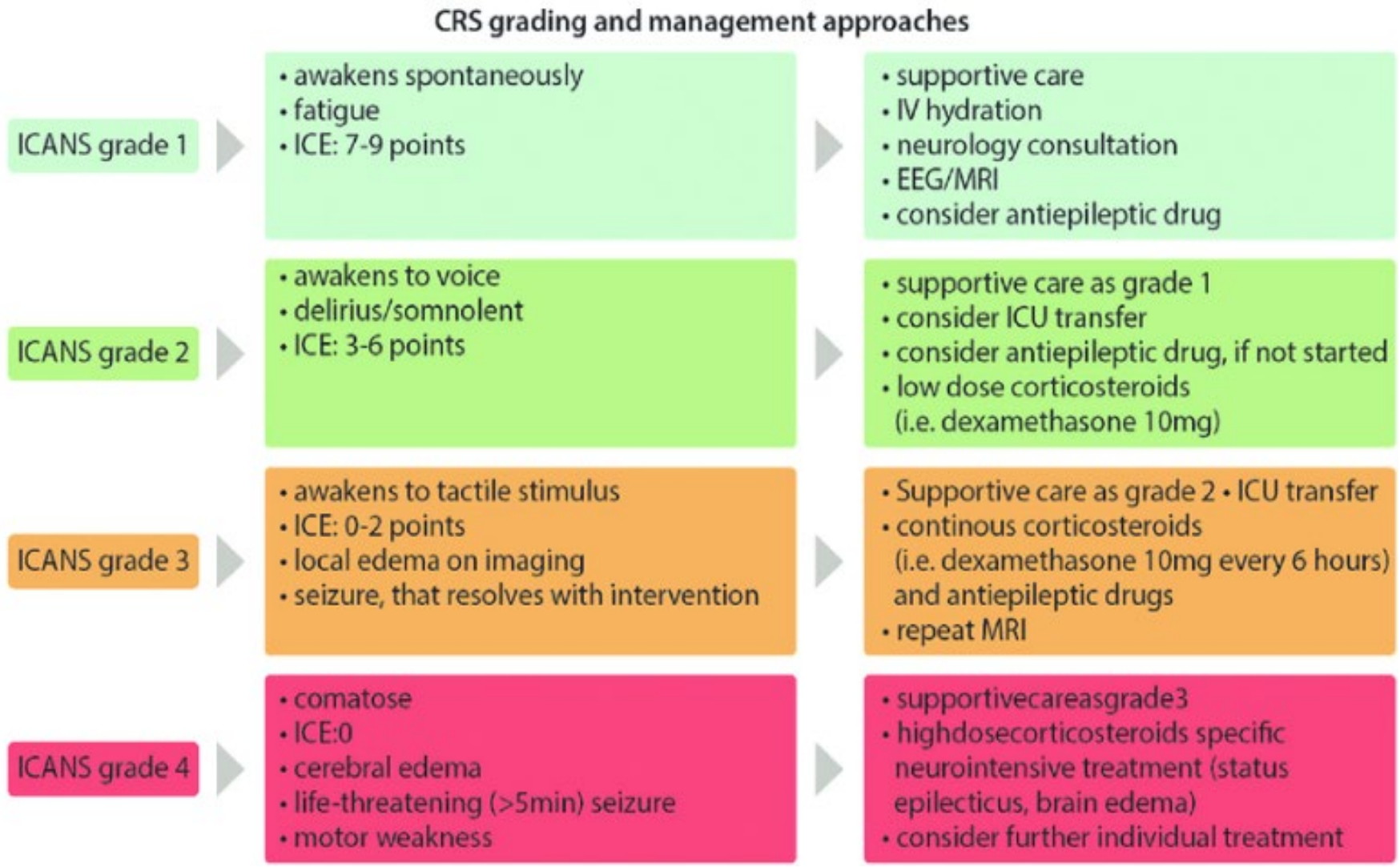
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Pathology unclear but most likely related to endothelial activation with BBB breakdown and passive diffusion of cytokines into the brain causing cortical irritation.

- Symptoms usually occur as CRS is resolving.

- ICE scoring: total of 10 points (done daily + Neuro exam)
  - Orientation: month, year, city, hospital (4 points)
  - Naming of 3 objects: clock, phone, pen (3 points)
  - Following commands: stick out tongue, close 1 eye (1 point)
  - Writing a sentence: Simple, standard (1 point)
  - Attention: Count backwards from 100 by 10 (1 point)

ICANS Grading/Management



(8) J.Borrega 2019

Neurologic Treatment Recommendations

Treatment for ICANS:

- Initiation of anti-seizure prophylaxis
- Steroids (low dose vs high dose) depending on severity/grade of neurologic toxicity.
  - Grade 1: Observe
  - Grade 2: Dexamethasone 10 mg q 12-24
  - Grade 3: Dexamethasone 10-20 mg q 8-12
  - Grade 4: Dexamethasone 10-20 mg q 6
- If cerebral edema present: HD methylpred 1-2 gm or 2mg/kg divided over 4 times per day

Other CAR-T Toxicities

Macrophage Activation Syndrome:

- Excessive production and multiplication of T cells and macrophages. Associated with severe CRS.

Tumor Lysis Syndrome:

- Metabolic complications due to the breakdown of dying cells. Can cause end organ damage.

B-Cell Aplasia:

- B cells destroyed leading to decreased ability to make antibodies that protect against infection. IVIG can be helpful.

Future Approaches

- Target other T cells (besides CD19)
- Tandem CAR-T
- T-Cell Fitness
- Allogeneic CAR-T: Need to use gene knock-out to avoid GVHD (use Campath).
- Check point resistant CARs and targeting surface proteins to help with solid organ tumors.

Summary

In summary, CAR-T therapy is a new treatment option that offers hope for patients with relapsed and refractory disease.

CAR-T therapies are changing the future of hematologic malignancies and are opening potential treatment pathways for multiple other hematologic and solid organ malignancies.

Thank you!

References

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(4) M Wang, J Munoz, A. Goy, et al. KTE-X19 CAR-T Cell Therapy in Relapsed or Refractory Mantle Cell Lymphoma N Engl J Med 2020: 382: 1331-1342.

(5) B. Long, L. Qin, B, Zhang, et al. CAR-T Cell Therapy for Gastric Cancer: Potential and Prospective Review. International Journal of Oncology: Feb 12, 2020; pages 889-899.

(6) A. Roche, C. Lagares, E. Elez, R. Roche. Cytokine Release Syndrome. Reviewing a New Entity in The Intensive Care Unit. Med Intensiva (Engl Ed). 2019 November; 43(8): 480-488.

(7) D. Lee, R. Gardner, D. Porter, et al. Current Concepts in the Diagnosis and Management of Cytokine Release Syndrome. Blood, 2014; (2): 188-195.

(8) J. Borrega, P. Godel, M. Ruger, O. Onur, A. Shimabukuro, M. Kochanek, B. Bol. In The Eye of the Storm: Immune Mediated Toxicities Associated with CAR-T cell Therapy. HemaSphere 3 (2), e191, April 2019. www.researchgate.net/figure/ICANS-grading.