CAR-T Cell Therapy: Patient Eligibility, Management, and Nursing Considerations

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Pediatric ALL

ALL is the most common childhood cancer

Almost all B-ALL expresses CD19 at diagnosis

~15% of patients relapse with conventional therapy

- Relapse often difficult to treat due to chemo resistance and dose limiting toxicities.
- Very little improvement over the past 20 years in survival rates for children who relapse

Need novel therapies: Targeted approach with CAR T cell therapy

Eligibility

Relapsed CD 19 + B ALL

Refractory CD 19 + B ALL

No curative options for therapy (ie. not eligible for BMT)

Cannot have rapidly progressing disease

> 6 months from BMT

No active GVHD and no immunosuppression

Cannot have active uncontrolled infection

CAR T Cell Therapy

Patient Population

- Patients in 1st relapse
- Majority are in 2nd or greater relapse
- Refractory to initial therapy
- Majority are refractory to multiple prior therapies

Goals for Therapy

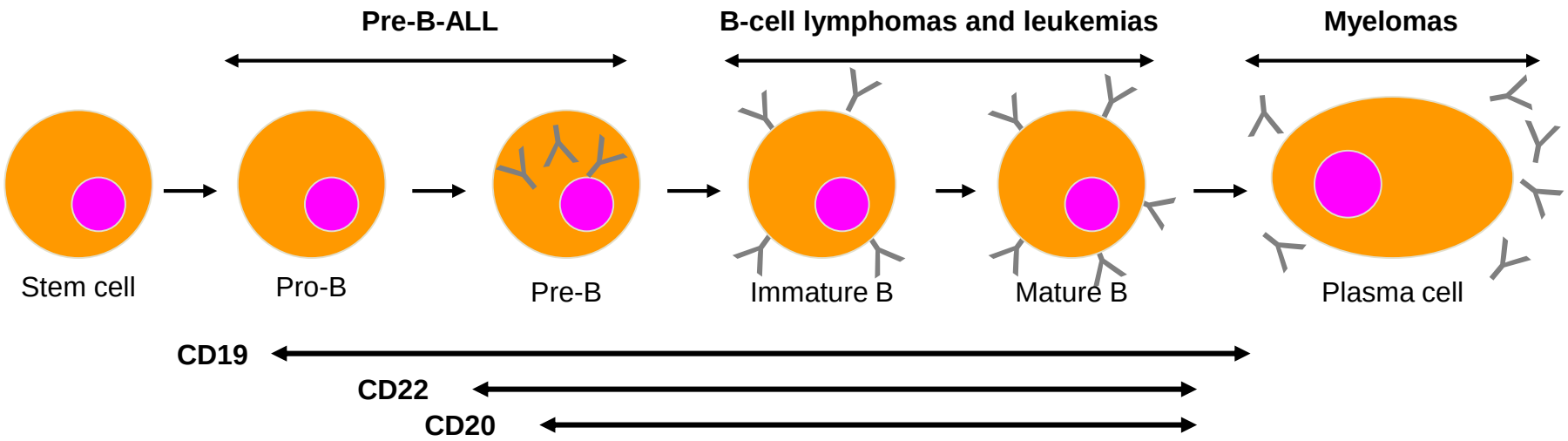
- **Proliferation**: high level of in vivo proliferation correlates with high response rates
- **Persistence:** longer term persistence may allow longer term disease control

In many cancers tumor specific antigens for target are not as well defined. But with ALL CD19 is a good target.

CD 19 is a protein widely expressed on normal and malignant B cells (from early pro-B stage through mature B cells)

The majority of cases of B-cell ALL are CD19 +

Stem cells do not express CD19



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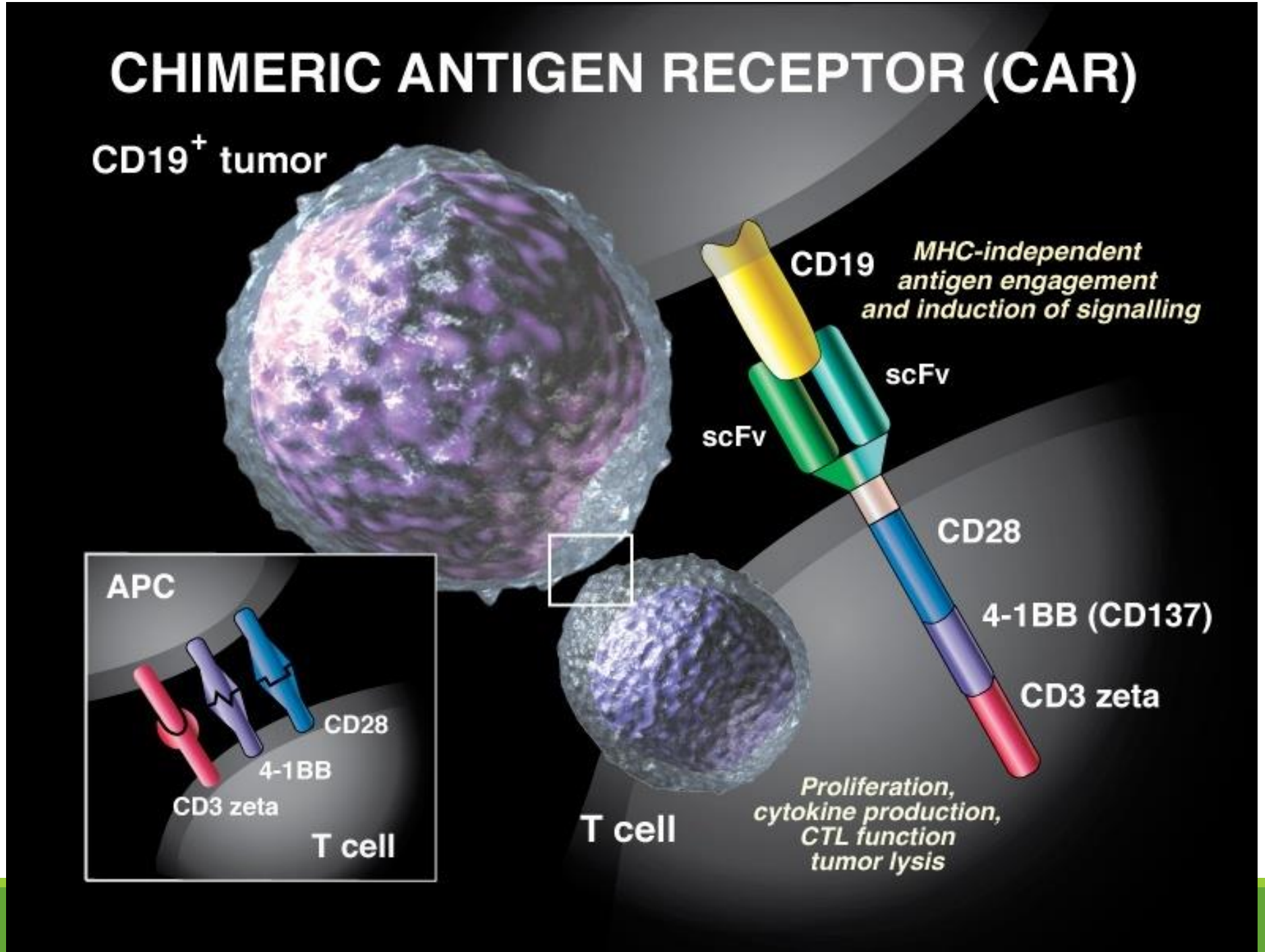

CHIMERIC ANTIGEN RECEPTOR (CAR)
CD19+ tumor
CD19
MHC-independent antigen engagement and induction of signalling
scFv
scFv
CD28
4-1BB (CD137)
CD3 zeta
APC
CD28
4-1BB
CD3 zeta
T cell
T cell
Proliferation, cytokine production, CTL function tumor lysis

Engineering Process

T Cell

- Type of lymphocyte
- Plays a central role in cell-mediated immunity
- Workhorses of the immune system. Recognize and attack invading disease cells.

Chimeric Antigen Receptor (CAR)

- Customized receptors with an extracellular antigen binding domain targeting antigens expressed on malignant cells combined with intracellular signaling domains of the T cell.
- Antigen binding domain derived from a monoclonal antibody single chain variable fragment.

Engineering Process

Lentiviral vector

- Vector is a tool used to deliver genetic material into cells
- Disabled HIV used as the vector

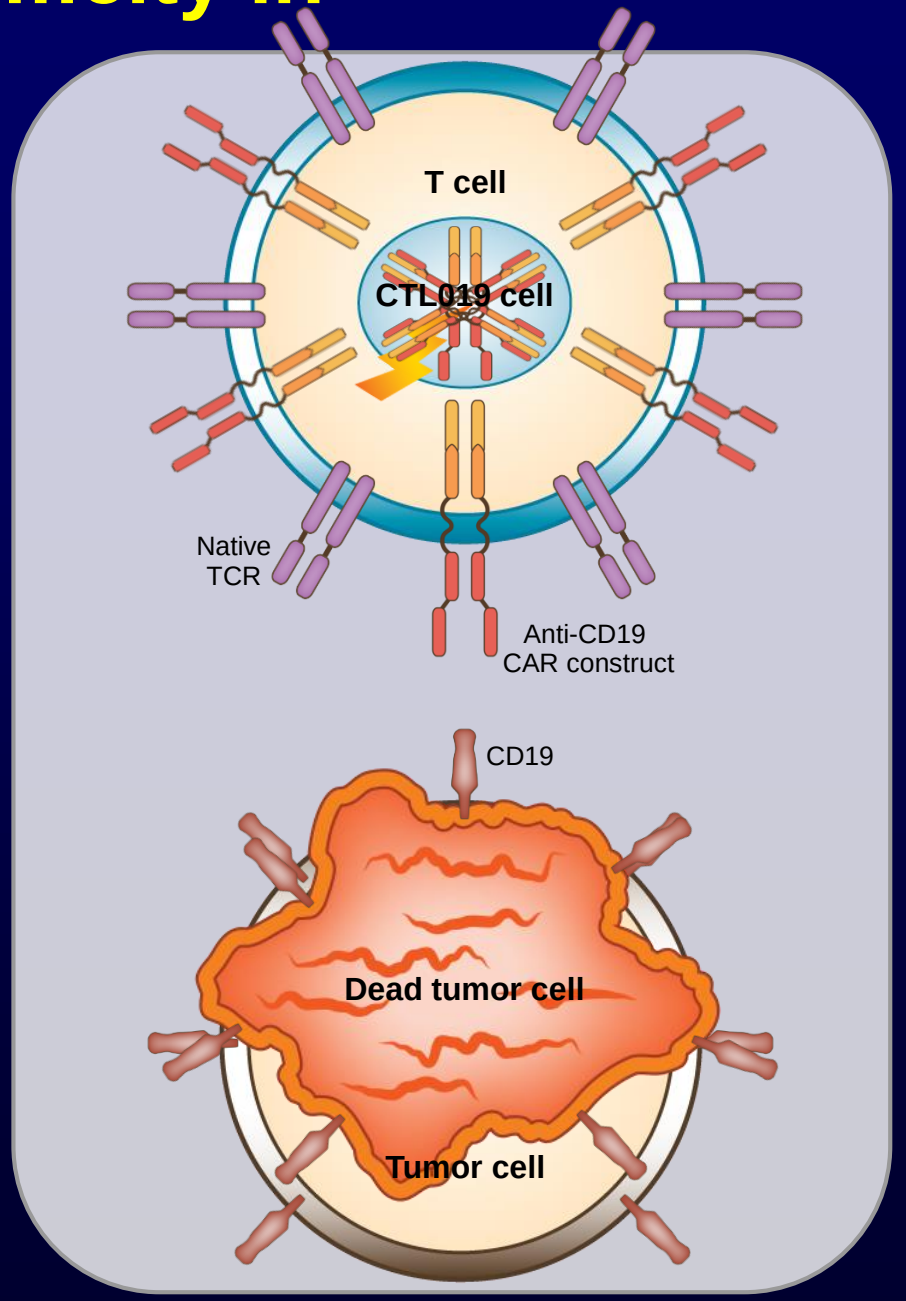
Genetic material is the chimeric antigen receptor with specificity for the CD19 antigen

Transduce T cells with lentiviral vector to express the CD19 chimeric antigen receptor

Using gene transfer techniques the T cells are modified to express antibodies against the CD19 antigen

Redirecting T cell Specificity in CTL019 cells

- CAR T cells engage an antigen on a tumor cell through the extracellular antibody domain. This activates the T cells.
- Engagement of the CAR T cell results in intracellular signaling and expansion of the CAR T cells to induce tumor cell killing
- CARs link an extracellular antigen recognition domain to intracellular signaling domains of the T cell.
- Intracellular signaling. Importance of 2nd costimulatory signal.
  - Increase expansion
  - Increase persistence
  - Increase potency
  - Prevent cellular exhaustion



Pre-Infusion Chemotherapy

Anti-leukemia

T cells expected to start expanding 7-10 days after infusion

Need to make sure leukemia is not out of control during that time frame

Cannot give chemotherapy once T cells infused

Lymphodepletion

Focus on administering T cells with robust proliferative capacity

Modulate host immune environment to support expansion and persistence

Adoptively transferred T cells engraft and expand more efficiently in a lymphopenic host

Presence of regulatory T cells must be minimized in both the patient and the infused cells.

CAR T Cell Infusion

- Pre-Meds (acetaminophen/diphenhydramine) ½ hour prior
- Infusion over few minutes
- Monitoring Vital Signs 1-2 hours post infusion

Response

Rapid onset of action

- Same as seen with chemotherapy or targeted therapy
  - Expect to see T cells expanding in 7-10 days

Infusions have resulted in 100 – 100,000 times proliferation/expansion of the engineered T cells after infusion into the patient.

CART cells found in marrow

CART cells found in CSF even if patients didn’t have CNS disease

Cytokine Release Syndrome

Constellation of inflammatory symptoms r/t T cell engagement and expansion

- Severity related to disease burden. Correlates with T cell proliferation.
- Can be mild to severe leading to multisystem organ failure
- Typically occurs 1-14 days after CAR T cell infusion
- Elevation in inflammatory markers. Massive elevation in IL-6.

Cytokine Release Syndrome

Fevers

Fatigue

Anorexia

Mylagias

Headaches

Hypotension

Capillary leak

Pulmonary edema

Coagulopathy

Renal dysfunction

Treatment

- Want to prevent multisystem organ failure but do not want to stop the T cells from working
- Supportive care
- Tocilizumab: Monoclonal antibody to IL-6 receptor. Blocks IL-6 mediated inflammatory effects.

Neurologic Side Effects

Encephalopathy

Confusion

Expressive aphasia

Delerium

Hallucinations

Tremors

Seizures

Tumor Lysis and GVHD

Tumor Lysis

Concern in patient with high blast load

Monitor electrolytes and uric acid

Allopurinol as needed

GVHD

Concern in patient who received a previous hematopoietic stem cell transplant

CART cells are most likely donor T cells

Activated T cells can cause GVHD

B Cell Aplasia (Off Tumor On Target Toxicity)

CART19 cells target and kill any cells expressing the CD19 antigen. Normal B cells express the CD19 antigen.

Hypogammaglobulinemia

- B cells are an important part of the immune system. Produce immunoglobulins. Inability to produce immunoglobulins increases risk of viral and bacterial infection
- Scheduled Immunoglobulin replacement: IV or Subcutaneous

B cell aplasia correlates with CAR T cell persistence

Relapse Post CAR T Cell Therapy

CD19+

- Short persistence of CAR T cells
- Evidenced by normal B cell recovery
- Immune mediated rejection ?
- Starting T cell quality. T cell exhaustion.

CD19-

- Due to antigen escape
- Is CD19 deleted/mutated/no longer expressed?
- Can happen even if CAR T cells still detected on research labs and with persistent B cell aplasia

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