Immunotherapy in Pediatrics AML: CART 33 Considerations during Pandemic

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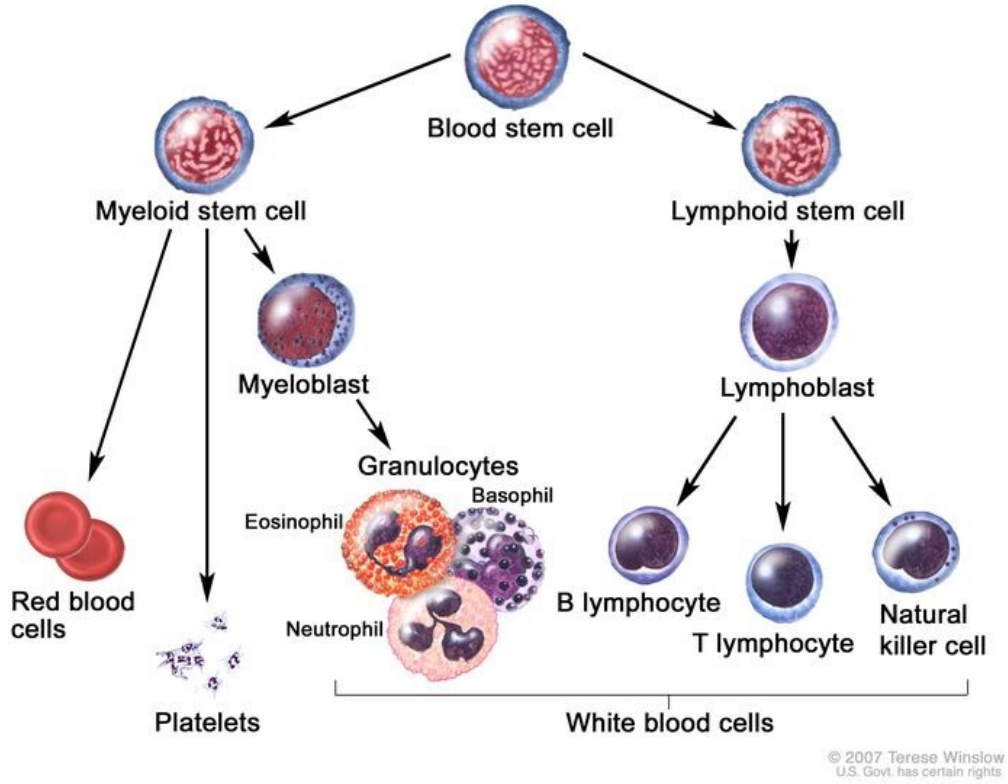
I have nothing to disclose and no conflict of interests

Case Study

- **LJ:** 18-year-old female, previously healthy
- **Presentation:** fatigue, shortness of breath, pallor
- **CBC: WBC:** 60,000 **Hemoglobin:** 6.0 **Platelets**: 550,000
  - Peripheral blasts
- **Bone marrow:** AML
- **CNS** : negative
- **Diagnosis**: AML ,monosomy 7, FLT -3 mutation

Acute myeloid leukemia (AML)

- Accounts for 20% of pediatric leukemias
- Peak incidence at 2 years of age and teenage years
- In US: ~ 730 cases : < 20 years of age annually
- FLT 3 mutations: ~ 20% pediatric patients



Siegel et al, Cancer Statistics, CA CANCER J CLIN 202171:7-33

Case Study

Treatment Regimens

- Cytarabine, daunorubicin, etoposide, IT cytarabine
- Cytarabine, fludarabine, gemtuzumab
- Clofarabine, etoposide, cyclophosphamide, Midostaurin
- Cytarabine, decitabine, venetoclax, IT cytarabine
- Gilteritinib

Side effects

- Febrile neutropenia
- Transfusion dependent
- Typhlitis
- C diff colitis
- Malnutrition: TPN
- Elevated LFTs

AML: Treatment

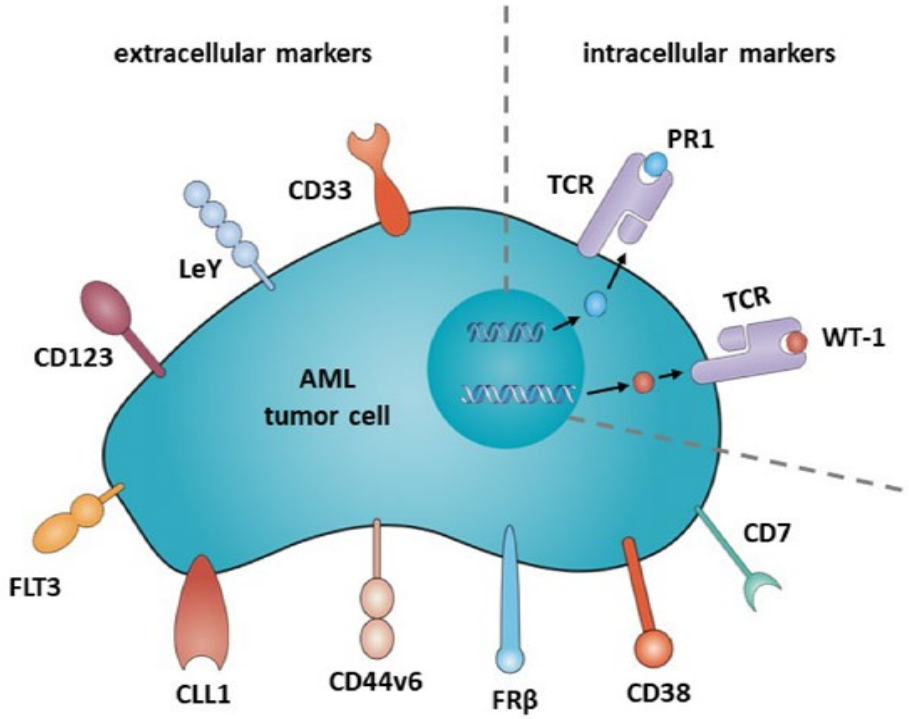
- Requires Intensive therapy
- 60-70% long term survival rate
- 1/3 patients will receive allogeneic HSCT in first remission
- 25-30% relapse
- Relapsed AML: often chemo resistant /refractory

NEED FOR NOVEL THERAPIES

Zwaan et al. J Clin Oncol. (2015) 33:2949-62

Targeted therapy

- FLT 3
  - Sorafenib
  - Midostaurin
  - Gilteritinib
- CD 33
  - Lintuzumab
  - Gemtuzumab ozogamycin



Picture: Hofmann et al, Journal of Clinical Medicine, 2019

CART for AML

- Potential targets: CD 33 and CD 123
  - Expressed on AML blasts
  - Expressed on healthy hematopoietic stem cells
- CD 33 and CD 123 directed CAR T cells: antitumor activity in preclinical model
- Limited clinical experience

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CD 33

- Cell surface glycoprotein
- Expressed on 80% of AML cells
- Higher expression associated with worse outcomes
- Expressed Kupffer cells in liver
- Expressed on normal hematopoietic cells

CD 33 CART in Children and Young Adults with r/r AML

- Primary objective:
  - Phase 1: trial to determine maximum tolerated dose of lentiviral transduced CD 33 CART in children and young adults with r/r AML

- Secondary objectives
  - Manufacturing, side effects, overall survival, event free survival, response rates, proceed to allo HSCT

ClinicalTrials.gov Identifier: NCT03971799

Clinical Timeline

Screening phase

- Referral
- Eligibility screening

Pre treatment phase

- Leukopheresis
- Bridging therapy
- Manufacturing

Treatment phase

- Baseline disease evaluations
- Lymphodepleting chemotherapy
- CD 33 CAR T infusion
- Monitoring for side effects
- Post Infusion evaluation

Screening

- CD 33 + AML
  - in second or greater relapse
  - post-transplant relapse
  - chemotherapy-refractory disease
  - CNS 3 disease excluded
- Age: ≥ 1 y/o -≤ 35 y/o
- Adequate organ function
- Adequate performance status

- Rapidly progressing disease excluded
- No active, uncontrolled infections
- > 100 days post single allo SCT
- No active Graft versus Host Disease (GvHD)
- Allo HCT donor identified

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Leukopheresis

- Collection/Manufacturing Challenges
  - Circulating AML blasts
  - Prior treatment impairs T cell function
  - Lymphopenia
  - AML blasts may limit T cell expansion

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Case Study

- **Bridging therapy:** Azacytidine, hydroxyurea
- **Pre-Infusion Disease Evaluations**: CNS: 1, BM: 45%
- **Lymphodepleting chemotherapy:** Fludarabine and cyclophosphamide
- **Day 0:** CART 33 infusion
- **Day 1:** fevers
- **Day 9-11:** fevers/hypotension
  - IVF, PRBCs
  - Tocilizumab

Monitoring for side effects

- Effects of lymphodepleting chemotherapy
- Cytokine release syndrome
- Neurotoxicity
- Sinusoidal Obstruction Syndrome
- Risk of bone marrow aplasia
  - Allogeneic HSCT identified
  - HCT 6-8 weeks post CD 33 infusion

ClinicalTrials.gov Identifier: NCT03971799

Considerations during Pandemic

- Safety of the patient on a clinical trial takes precedence
- Risk/benefits of modifying treatment
- COVID screening
- Monitoring for side effects
  - Fever
  - Increased complication of respiratory virus in immunosuppressed
- Research Specimens: Processed for patient safety
- Potential impact of COVID 19 on available blood supply

Considerations during Pandemic

- Staff alternate work arrangements
- Protocol modifications
- Unavoidable deviations
- Alternative methods for assessments
  - Phone
  - Telemedicine visits

C. Paterson et al. Seminars in Oncology Nursing 36(2020) 151028

Considerations during Pandemic

- Consolidation of services
- Educating staff
- Consistent plan
- Family lodging
- Visitor limitations
  - Stay at home, quarantine, travel bans

Case Study

- Day 11: afebrile, VSS, blood cultures negative → discharged
- Daily follow up in clinic through day 14
- Day 14-28: clinic follow up 2-3 x week
  - Transfusion dependent
  - Increasing WBC
  - Peripheral blasts
- Day 28: Progressive Disease: MRD: 65%
- Returned home for additional therapy

Questions