Is Childhood Leukemia Curable? Challenges and Milestones in Current Approaches

Nirali N. Shah, MD
Associate Research Physician
Pediatric Oncology Branch
National Cancer Institute
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Disclosures

- No disclosures to report
Educational Objectives

• Provide a general overview of pediatric ALL and current treatment approaches

• Review advances in immunotherapeutic approaches for treatment of ALL

• Discuss future directions and challenges in immunotherapy for ALL
Lets meet our special guests...

***All patients/parents have provided consent/assent or permission as appropriate to share their pictures and their stories***
BJ

- 18 year old male
- Diagnosed in October 2015
- Previously healthy
- No known risk factors
- Friend to all, loved son and brother
- Came to the NIH at age 19

Images courtesy of BJ’s mother
MM

- 3 ½ year old female
- Diagnosed in March 2012
- Previously healthy
- No known risk factors
- Loves to dance, and is the heart and soul of her family
- Came to NIH at age 8

*Images courtesy of MM’s parents*
Sunny

- 6 year old male
- Diagnosed in June of 2010
- Previously healthy
- No known risk factors
- Loves X-box, food, challenges and is a loving brother and son
- Came to the NIH at age 12

Images courtesy of Sunny's parents
What are Lymphoblasts?
Childhood Acute Lymphoblastic Leukemia (ALL)

- Most common cancer diagnosed in children.
  - 41 cases/million in children aged < 14
  - 17 cases/million in teens between ages 15-19
  - 25% of all new cancer diagnosis

- 85-90% of patients will be cured.

- “Poster-child” for efficacy and importance of cooperative groups and clinical trial participation.

Data courtesy of GH Reaman, H Sather, Children’s Oncology Group
Origin of ALL Therapy

• Based on the observation of folic acid agonists leading to an “acceleration” of leukemia progression
• This report outlined the cases of 5 children who attained a temporary remission with use of folic acid antagonists
Current Treatment Plan

- Combinatorial chemotherapy treatment strategy with non-competing mechanisms of action.
- Series of intensified/de-intensified treatment cycles.
- Prolonged maintenance phase (2-3 years)
- Risk-adapted approach
Risk Factors

- Standard NCI
  - Age 1-10 years
  - White blood cell count < 50,000
- Central nervous system disease
- Testicular involvement
- Down syndrome
- Sex
- Race/Ethnicity
- Immunophenotype (B v T-cell)

- Cytogenetics
  - Ph+; t(9;22)
  - MLL/KMT2A; 11q23
  - ETV6-RUNX1; TEL-AML; t(12,21)
  - Hypo/hyperdiploid
- Newcomers:
  - Ph+ like
  - iAMP21

- Response to therapy
Challenges

• Curative options for relapsed/refractory disease remains a therapeutic challenge

• Outcomes for the adolescent young adult (AYA) population remain particularly poor

• Toxicity from cumulative therapy not insignificant

• Novel therapies are needed
Our Patients

BJ
• High-risk by age and presenting WBC (121K)
• Response to chemotherapy was suboptimal:
  • End-induction + disease → high risk arm
  • Disease burden increased after consolidation

MM
• Standard risk at presentation
• Response to chemotherapy was suboptimal:
  • End-induction + disease → high risk arm
  • Continued on therapy
• Relapsed in 2014 with CNS only disease

Sunny
• Standard risk at presentation
• Relapsed towards the end of therapy in September 2013
Novel Therapies: FDA Approval

- Clofarabine: Purine nucleoside antimetabolite
- Nelarabine: Purine nucleoside antimetabolite, T-cell
- Vincristine Sulfate Liposome Injection (Marqibo®): ALL, in adults

- Complete remission rates: +/- 20%
**B Cell Surface Antigens**

**Antigen Independent**
- TDT
- CD19
- CD79a
- Pax-5
- CD10
- HLA-DR
- Cytoplasmic Ig
- Surface Ig
- CD38

**Antigen Dependent**
- CD20
Immunotherapy for ALL

Portell C. Leukemia & Lymphoma 2013
Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O’Brien, M.D., Xiongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendriess, M.D., Ph.D., and Anjali S. Advani, M.D.

- Pediatric: Retrospective study presented at ASCO 2017
- Phase II COG Study planned
Blinatumomab

- 50-70% CR rate in adults
- 30-40% CR rate in children
Novel Therapies: FDA Approval

- Inotuzumab: Approval in 2017, adults only

- Complete remission rates: +/- 40-50%
CAR-T Cell Therapy

• What is a CAR
  • Chimeric Antigen Receptor

• Retains the functionality of a T-cell with the antigen recognition properties of antibody

• Customized receptor
  • Extracellular antigen-binding domain
  • Intracellular signaling domain of T cells
Making a CAR-T Cell

1. Patient undergoes apheresis for collection of lymphocytes

2. Lymphocytes are put into culture, stimulated and transduced (lenti/retrovirus)

3. Cells expand in vitro

4. Patient receives lymphodepleting chemotherapy prior to cell infusion

5. CAR-T Cell infusion on Day 0

Infusion Day!!

Bench to Bedside
Cytokine Release Syndrome

- Neurologic:
  - Headaches
  - Changes in level of consciousness
  - Delirium
  - Aphasja
  - Apraxia
  - Ataxia
  - Hallucinations
  - Tremor
  - Dysmetria
  - Myoclonus
  - Facial nerve palsy
  - Seizures

- Constitutional:
  - Fevers
  - Rigors
  - Malaise
  - Fatigue
  - Anorexia
  - Arthralgias

- Cardiovascular:
  - Tachycardia
  - Widened pulse pressure
  - Hypotension
  - Arrhythmias
  - Decreased left ventricular ejection fraction
  - Troponinemia
  - QT prolongation

- Pulmonary:
  - Tachypnea
  - Hypoxia

- Renal:
  - Acute kidney injury
  - Hyponatremia
  - Hypokalemia
  - Hypophosphatemia
  - Tumor lysis syndrome

- Gastrointestinal:
  - Nausea
  - Emesis
  - Diarrhea

- Musculoskeletal:
  - Myalgias
  - Elevated creatine kinase
  - Weakness

Brudno/Kochenderfer Blood 2017
CD19 CAR Clinical Updates

Maude et al. NEJM 2014
90% CR rate (not ITT)
All with CRS

Lee et al. Lancet 2015
67% CR rate (ITT)
All responders with CRS

Novartis sponsored global CD19 CAR registration
trial (“ELIANA”)
82% (41 of 50) patients achieved CR
65% CR on ITT
CAR Therapies: FDA Approval

• Kymriah™ (tisagenlecleucel, Novartis): For children up to age 25 with ALL (August 2017)

• Tocilizumab: To treat CAR T-cell related CRS (August 2017)

• Yesclarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)

• Complete remission rates: +/- 50-80%
Will CD19 CAR be “THE” Answer?

NO ONE FIGHTS ALONE.

CAR-T in April 2012
Oh Where... Oh Where... Has my CD19 gone?

- At least ONE identified mechanism:
  - Loss of the surface epitope, but retention of the target protein (in part)
  - Due to clustering of nonsense and missense mutations in exon 2 of CD19
  - Specific frameshift mutation eliminates full-length CD19 but allows expression of an isoform
    - Mostly cytosolic and hidden from T cells
  - Hallmark of relapsed leukemia post CAR was lack of the full-length isoform

*Sotillo/Thomas-Tikhonenko, Cancer Discovery 2015*
Lineage Switch (ALL $\rightarrow$ AML)

- *MLL*-rearranged B-ALL (11q23) rearrangement
  - “Infant” ALL $\rightarrow$ VERY poor prognosis

- Gardner et al.
  - 7 of 7 with *MLLr*-ALL attained MRD neg CR post –CD19 CAR
  - Relapses seen in 2 with myeloid phenotype

- Similar experience seen in *MLLr*-ALL treated with blinatumomab

- Jacoby et al.
  - CD19 CAR immune pressure induces lineage switch
CD22 on ALL

- 140 kDa B-lineage differentiation antigen
- Expressed on vast majority of pre-B ALL
- Targetable antigen for immunotherapy
  - Epratuzumab
  - Inotuzumab
  - Moxetumomab (HA22)
Characterization of CD22 Expression in Acute Lymphoblastic Leukemia

Nirali N. Shah, MD,1,2* Maryalice Stetler Stevenson, MD, PhD,2 Constance M. Yuan, MD, PhD,2 Kelly Richards, RN,1 Cindy Delbrook, RN,1 Robert J. Kreitman, MD,3 Ira Pastan, MD,3 and Alan S. Wayne, MD,1,3,4

TABLE I. Characteristics of CD22 Expression on Patient Samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual casesa</td>
<td>163</td>
</tr>
<tr>
<td>Median age of subjects (range), years</td>
<td>12.5 (0.6–25)</td>
</tr>
<tr>
<td>Median site density (range), sites/blastb</td>
<td>3,470 (349–19,653)</td>
</tr>
<tr>
<td>Median % CD22 expression (range)c</td>
<td>100% (22%–100%)</td>
</tr>
<tr>
<td>Cases with less than 90% CD22 expressionc</td>
<td>7</td>
</tr>
</tbody>
</table>

a337 samples analyzed from 163 individual subjects. 73 had serial evaluations, many with multiple samples, inclusive of 47 subjects who received treatment with anti-CD22 immunotoxin therapy. b160 of 163 samples had site density evaluable for analysis. c162 of 163 subjects had CD22% available for analysis.
MLL-rearranged ALL

- Lower CD22 Site Density
- Partial positivity may be seen
Anti-CD22 CAR Construct

• Second generation CAR
• Utilizes m971 anti-CD22 scFv
• 4-1BB/CD3-zeta signaling

Haso et al, Blood 2013
NCI CD22 CAR Protocol

• Phase I, 3+3 dose escalation, CD22+, ages 1-30

• NCI-construct (41BB/m971)

• Enrolled first patient in 2014

• Lymphodepletion:
  • Fludarabine 25 mg/m²/day x 3 days (Days -4 to -2)
  • Cyclophosphamide 900 mg/m²/day x 1 days (Day -2)

Haso et al. Blood 2013
ClinicalTrials.gov NCT02315612
CD22 CAR is Active in CD19^{neg/dim/+} ALL

- Complete remission rate: 73%
- Limited CRS (Grades 1 & 2)
- Limited neurotoxicity
- Relapse associated with modulation in CD22**
## Dose Escalation

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Transduced CAR-T cells/kg</th>
<th>n</th>
<th>Dose Limiting Toxicity</th>
<th>Complete Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$3 \times 10^5$</td>
<td>6</td>
<td>1 (Gr 3 diarrhea)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>2</td>
<td>$1 \times 10^6$</td>
<td>3</td>
<td>None</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>3</td>
<td>$3 \times 10^6$</td>
<td>2</td>
<td>1 (Gr 4 hypoxia)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>2</td>
<td>$1 \times 10^6$</td>
<td>3*</td>
<td>None</td>
<td>1/3 (33%)</td>
</tr>
</tbody>
</table>

Expansion at Dose Level 2: $1 \times 10^6$ CAR T cells/kg

*1 patient with DLBCL
### Patient Characteristics (n=22)

<table>
<thead>
<tr>
<th>Dose level 2: $1 \times 10^6$ CAR-T cells/kg</th>
<th>n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, (range)</td>
<td>17.5 (4-30)</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>15 (68%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo HSCT</td>
<td>18 (82%)</td>
</tr>
<tr>
<td>Anti-CD19 therapy</td>
<td>20 (91%)</td>
</tr>
<tr>
<td>Anti-CD22 CAR</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19 negative/dim</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>$\geq$ M2 marrow</td>
<td>17 (78%)</td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>
Our Patients

BJ
- Received blinatumomab and achieved remission
- Went to hematopoietic stem cell transplant (HSCT)
- Relapsed with CD19 dim disease

MM
- Relapsed again
- Received CD19 CAR T cells and went to HSCT after achieving remission
- Relapsed with CD19 + disease

Sunny
- Received CD19 CAR T cells and went to HSCT after achieving remission
- Relapsed almost 2 years post HSCT with CD19 negative disease
Complete Remission Rate: 78% (17/22)

- Longest remission is > 2 years post-CAR
- For those with relapse, generally 6+ months post-CAR
- Intensified lymphodepletion** → MRD neg CR

Individual ALL patients (n=21)
CD22 Antigen Expression at Relapse

• 5 patients with relapse
  • 1—CAR cell loss (dose level 1)
  • 4—with changes in CD22
    • 2 with relapse at 6 months
    • 2 with relapse at 2 months*

• Changes in CD22
  • Decrease in Site Density (n=2)
  • Antigen loss (n=1)
  • Both (n=1)

• *Received prior anti-CD22 targeted therapy
Experience to Date

• First successful salvage CAR therapy for CD19 negative B-ALL
• Preliminary experience suggests comparable potency to anti-CD19 CAR
• Response correlated with dose level
• No severe or irreversible neurotoxicity
• Relapse associate with changes in CD22 expression level
• Future Directions: Opportunities for multi-specific CAR targeting
Bedside to Bench

Our Patients Inspire Change
Manufacturing Changes

• Variability in product composition between patients
• Despite this, we had successful manufacturing of products in > 90% of subjects
• We could not manufacture cells for BJ
• In conjunction with the CC Cell Processing Section, we incorporated CD4/CD8 bead selection for the product
• This led to successful manufacture of the product
• We are now using this for all patients
• Early experience suggests that this may increase the potency of the cells

Images courtesy of BJ's mother
Intensified Lymphodepletion

• Sunny’s first cell infusion led to an incomplete response.
• Second CAR-T cell infusions are generally ineffective.
• We modified the protocol to try an intensified lymphodepletion strategy... it **Worked**.
• We now use this for all second infusions moving forward.
The “One-Two” Punch

• Attained a complete remission but relapsed at approximately 6 months post CAR with CD19+/CD22 dim disease.
• Single antigen approach likely not sufficient for a sustained remission.
• We are currently weeks away from our Bi-specific CAR trial being open to enrollment.
Phase 1 Dose Escalation Study of Anti-CD19/CD22 Chimeric Antigen Receptor (CAR) T Cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B Cell Malignancies

- Hypothesis: Simultaneous targeting of CD19 and CD22 could diminish the risk of antigen loss escape
- Novel bivalent, bispecific CAR to be tested in the clinic
- Planning to open February 2018

Activity of Bispecific CAR: *In vivo* activity against CD19+/22+ B-ALL

Data Courtesy of Haiying Qin
Acute Myelogenous Leukemia (AML)

- 20% of all childhood leukemia
  - Childhood AML is 6% of all AML

- Overall survival: 60-70%

- Cytogenetics have an essential role in diagnosis and prognosis

- Intensive therapy is associated with high risk of infectious complications (5-7% treatment related mortality)

- Relapse is the greatest cause of failure
  - 30-40% relapse rates

![Improved Survival by Era](chart)
AML, A New Frontier of CAR Therapy

- Outcomes for AML ~ 50-70% overall survival
- Immunophenotype more variable
  - CD33 (gemtuzumab target)
  - CD123
- B-cell aplasia as a consequence of CD19 targeted therapies can be supported
- Myeloid aplasia as a consequence of myeloid antigen targeted therapies, however, is much more difficult to manage
  - May need immediate stem cell transplantation to restore aplastic marrow
Will CARs be “THE” Answer?

- Fatal Neurotoxicity (or CRS)
- Not for Everyone
- Antigen Loss
- Inability to Manufacture Cells
- CAR Cell Failure

30-40% Relapse Rate
Future Directions

- Novel CAR constructs:
  - AML CAR
  - Bi-specific CAR

- Optimizing second infusions

- Improving CAR persistence

- Increasing tumor sensitivity by enhancing antigen expression

- Bringing CAR constructs earlier into the therapeutic plan

- Exploring response in lymphoma and CNS disease

- Decreasing toxicity

- Improving access to therapy
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• ..and so many more

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