Title
Perspectives of Immunotherapy for Lymphoma: A focus on Chimeric Antigen Receptor T-Cell Therapies

Date:

Elizabeth Budde, MD, PhD
Department of Hematology & HCT
Beckman Research Institute
City of Hope National Medical Center
Duarte, CA
DISCLOSURES

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Advisory board and / or Speaker Bureau:
Promab Biotechnologies, AstraZeneca, Genentech, Roche, KITE Pharma, and Gilead Inc.
Why does the immune system fail to eliminate cancer?
Immunoediting and Tumor Development

The immune system is unable to eradicate or control cancer cells when:

1. T-cells are unable to recognize tumor cells as foreign
2. Tumor-specific T-cells are deficient in number
3. T-cells are unable to function properly

Exhausted T-cell
Goal of Immunotherapy

• To exist, tumors must evolve mechanism to locally disable and/or evade the immune system.
• The **goal** of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.
Immunotherapy in Clinical Oncology

- **1980**: IFN-α or IL-2 (Immune cell Booster)
- **1990**: Target specific Abs (Rituximab, Herceptin, brentuximab, etc)
- **2000**: Therapeutic vaccines (Checkpoint blockers: ipilimumab, pembrolizumab, nivolumab, atezolizumab, etc)
- **2010**: Targeted Cell therapy (Provenge (prostate Ca), T cell engagers, CAR T: Blinatumomab KTE-019, CTL-019)

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- **2010**: Targeted Cell therapy (Provenge (prostate Ca), T cell engagers, CAR T: Blinatumomab KTE-019, CTL-019)
What are CAR and CAR T-cells?

• CAR = protein on the surface of the cell that contains:
  1. Portion outside the cell: binds to a protein on the tumor cell surface
  2. Portion inside the cell: necessary “on” switches to activate the T cell
     • These differ between the different CAR T cells
• CAR T-cells = T cells with the CAR protein expressed on the cell surface
CAR T Cell Therapy: A Living Drug

- Genetic modification of T cells to redirect them to become robust tumor specific T cells.
Adoptive Therapy Using CAR T Cells

CAR T cell manufacturing and release testing: 17 to 22 days

Leukopheresis: 1 day

Supporting Tx

Lymphodepletion: 5 days

T cell infusion

Acute toxicity monitoring and management: 8 weeks
## Landscape of CAR T Cell Trials

Total = 836  
US: 333  
China: 283  
Europe: 125

<table>
<thead>
<tr>
<th>Disease</th>
<th>US</th>
<th>CHINA</th>
<th>EUROPE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYMPHOMA</td>
<td>97</td>
<td>123</td>
<td>25</td>
<td>245</td>
</tr>
<tr>
<td>ALL</td>
<td>44</td>
<td>52</td>
<td>10</td>
<td>106</td>
</tr>
<tr>
<td>CLL</td>
<td>29</td>
<td>28</td>
<td>5</td>
<td>62</td>
</tr>
<tr>
<td>MM</td>
<td>28</td>
<td>30</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>AML</td>
<td>7</td>
<td>12</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>
Anti-CD19 CAR T cells in Aggressive B Cell Lymphoma

**KITE: ZUMA-1**
- Median follow-up 27.1 mo
  - ORR 83%
  - CR 58%
  - Ongoing CR 35%
- CRS grade ≥ 3: 11%
- NT grade ≥ 3: 32%

**Novartis: JULIET**
- Median follow-up 19 mo
  - ORR 54%
  - CR 40%
  - Ongoing CR 37%
  - 66% RFS at 6 mo; 64% at 12, 18 mo.
- CRS grade ≥ 3: 23%
- NT grade ≥ 3: 12%

**JUNO: TRANSCEND (CORE)**
- Median follow-up 6 mo
  - ORR 78%
  - CR 54%
  - Ongoing CR 44%
- CRS grade ≥ 3: 1%
- Full cohort
- NT grade ≥ 3: 13%

ASH 2018; ASCO 2018
Shuster et al. NEJM 2019
Locke et al. Lancet Oncology 2019
Indication
Adult pts with rel/ref DLBCL after ≥ 2 lines, tFL, High grade B cell lymphoma primary mediastinal B cell lymphoma

Price
$373,000 per product

Approved on 10/18/2017

Indication
Adult pts with rel/ref DLBCL after ≥ 2 lines, tFL, High grade B cell lymphoma

Price
$373,000 per product

Approved on 5/1/2018
## Real World experience with Axi-cel

<table>
<thead>
<tr>
<th></th>
<th>6 center experience (N = 136)</th>
<th>17 center experience (N = 295)</th>
<th>ZUMA-1 (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>61 (21-79)</td>
<td>58 (64-77)</td>
<td>58 *23-76)</td>
</tr>
<tr>
<td>Prior ASCT %</td>
<td>30</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Bridging therapy %</td>
<td>57</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>T cell not infused</td>
<td>13 (9.6%)</td>
<td>21 (7.1%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td></td>
<td>6 PD</td>
<td>12 PD</td>
<td>1 PD</td>
</tr>
<tr>
<td></td>
<td>1 CR</td>
<td>1CR</td>
<td>2 CR</td>
</tr>
<tr>
<td></td>
<td>3 product failure</td>
<td>7 product failure</td>
<td>1 product failure</td>
</tr>
<tr>
<td></td>
<td>2 infection; 1 others</td>
<td>1 infection</td>
<td>6 AEs (1 death)</td>
</tr>
<tr>
<td>Not Meet ZUMA-1 Criteria %</td>
<td>62%</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Best ORR % day 30</td>
<td>74</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Best CR %</td>
<td>49 (ITT 44)</td>
<td>47 (ITT 44)</td>
<td>52 (ITT 47)</td>
</tr>
<tr>
<td>CR % at day 90</td>
<td>n/a (53 at month 6)</td>
<td>57</td>
<td>58</td>
</tr>
</tbody>
</table>

ASH 2018
A DLBCL patient on ZUMA-1

Pre CAR T treatment
Feb 11, 2016

Post CAR T treatment
Mar 31, 2016
Case report: COH Yescarta Experience

49 yo woman
-refractory double hit high grade B cell lymphoma
-5 lines of chemo; XRT x 3

Pre-treatment
12.11.2017

Post-treatment
1.17.2018
## What’s on the Horizon? CD19CAR T

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Study (N)</th>
<th>CARs</th>
<th>CR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantle cell lymphoma</td>
<td>ZUMA-2</td>
<td>KTE-x19, JCAR017</td>
<td>n/a (n = 80) 53% (9/17)</td>
</tr>
<tr>
<td></td>
<td>TRANSCEND NHL 001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>TRANSCEND NHL 001 City of Hope</td>
<td>Liso-cel NHL3</td>
<td>44% (4/9) -ASH 2019</td>
</tr>
<tr>
<td>CLL</td>
<td>TRANSCEND CLL 004</td>
<td>Liso-cel</td>
<td>46% (10/22)</td>
</tr>
<tr>
<td>iNHL</td>
<td>FHCRC UPENN ZUMA-5 BELINDA</td>
<td>JCAR014 CTL-019 Axi-cel Tisa-cel</td>
<td>88% CR (7/8) 71% (10/14) n/a (n = 80) n/a</td>
</tr>
</tbody>
</table>

## What’s on the Horizon?

### Other targets

<table>
<thead>
<tr>
<th>Disease</th>
<th>B cell NHL</th>
<th>T cell lymphoma</th>
<th>Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targets (in the clinic)</strong></td>
<td>CD20CAR, CD19/CD20 CAR, CD22 CAR, CD19/CD22 CAR, ROR-1 CAR</td>
<td>CD4 CAR, CD5 CAR, CD30 CAR</td>
<td>CD30 CAR</td>
</tr>
<tr>
<td><strong>Targets (Preclinical)</strong></td>
<td>BAFF CAR, Kappa CAR</td>
<td>CD7 CAR, CCR4 CAR, CD37 CAR</td>
<td>CD123 CAR</td>
</tr>
</tbody>
</table>
CAR T Cell Therapy: Complications

Commonly reported important adverse events

- On target off tumor effects, i.e. B cell aplasia (CD19CAR)
- Lymphodepletion chemo-related toxicity
- Tumor lysis syndrome
- Macrophage activation syndrome (HLH/MAS)
- Coagulopathy
- Cytokine release syndrome
- Neurotoxicity
- Infection
- Prolonged pancytopenia
Cytokine Release Syndrome

- A constellation of inflammatory symptoms from cytokine elevations.
- Association with T cell activation and proliferation
- Association with clinical benefit and toxicity
CAR T cell therapy is not benign

<table>
<thead>
<tr>
<th></th>
<th>ZUMA-1 KTE-019</th>
<th>JULIET CTL-019</th>
<th>TRANSCEND JCAR17 core group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS grade ≥ 3</td>
<td>12%</td>
<td>23%</td>
<td>0% (n=29)</td>
</tr>
<tr>
<td>Grading Median TTO</td>
<td>Lee’s 2d (1 - 12)</td>
<td>Penn scale 3d (1 - 9)</td>
<td>Lee’s 5d (1 - 14)</td>
</tr>
<tr>
<td>NT grade ≥ 3</td>
<td>31%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Grading Median TTO</td>
<td>CTCAE4.03 5d (1 - 17)</td>
<td>CTCAE4.03 n/a</td>
<td>CTCAE4.03 10d (3 - 23)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>0%</td>
<td>26%</td>
<td>20% (4/20)</td>
</tr>
</tbody>
</table>

ASH 2017
A Case of CRS

Cy/Flu  
D-5 to -3  
200M CAR T cell infusion

200M CAR T cell infusion  
D0  
D1

Tocilizumab: D5, D6, D7; Dex:D6, D8

D5  
D6 hypoxia, intubation, BAL-> adenovirus

D8

D10 extubation

Ferritin (ng/ml)

CRP (mg/L)
Neurologic Toxicity

D0
Teresa and I love Jesus

D3
Teresa and I love Jesus

D6
Teresa and I love Jesus

D14
Teresa and I love Jesus

D21
Teresa and I love Jesus

D28
Teresa and I love Jesus
### Infection: Dancing with the devil

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient N</th>
<th>All Grade</th>
<th>Severe (≥ grade 3)</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC</td>
<td>113</td>
<td>31%</td>
<td>14%</td>
<td>2% (n = 3)</td>
</tr>
<tr>
<td>Kymriah</td>
<td>174</td>
<td>55%</td>
<td>33%</td>
<td>1% (n = 1)</td>
</tr>
<tr>
<td>Yescarta</td>
<td>108</td>
<td>38%</td>
<td>23%</td>
<td>0% (n = 0)</td>
</tr>
</tbody>
</table>

**ID prophylaxis is recommended**
- lack of standard approach
- autoHCT guideline
- anti-fungal prophylaxis in pts with prior HCT

CAR T Cell Therapy: Challenges

Even superheroes have to do their homework!
CAR T Cell Therapy: Challenges

How to make CAR T more available for patients with

✔  **Highly aggressive disease**
   - products with short manufacturing time
   - off the shelf products (iPSC, NK-CAR, AlloCAR).
     Clinical trials (CD19CAR NK, PBCD19CAR, UCAR)

✔  **Poor performance status and lack of reserve**
   - Novel CAR design with preserved efficacy but less cytokine production or nontoxicity (less toxic). i.e. Autolus trials
   - Optimize the manufacturing platform (cytokines, T cell subsets, etc).
   - Optimize management of CRS and neurotoxicity
     ZUMA-1 new cohort with preemptive steroids
     Use of Anakinra, dasatinib, etc.
CAR T-cell Therapy: Challenges

✓ Post CAR T relapse or non-responders
CAR T-cell Therapy: Challenges/next step

- Post CAR T relapse or non-responders

Potential resistance mechanism
- Unfit CAR T product
  - Armored CARs
  - ibrutinib (CLL pt)
  - PI3Ki (BB21217)
  - iMiDs (ZUMA-14, PLATFORM)
  - 4-1 BB agonists (ZUMA-11)

- Tumor cell/environment
  - Add PD-1/PD-L1 blockade
    - (ZUMA-6, PLATFORM, Auto-3)

- Antigen/epitope escape
  - ~25% NHL relapse
  - Epitope loss; ↓ expression

Dual targeting
  - (i.e. CD19/22, CD19/20, CD19/BAFFR)
CAR T-cell Therapy: Challenges

Post CAR T relapse or non-responders, What to do at the present time?

- 30 yo F with c-myc and Bcl-2 double expressor DLBCL
- 6 x RCHOP -> CR
- Relapsed 8 months later. R-ICE x 2 -> CR; BEAM-autologous stem cell transplant;
- Relapsed 3 months later. CD19CAR T cell treatment

Biopsy: D19+, CD20+

Clinical trial

Bispecific ab

Pre-CAR Tx

D40

D187

C3D4 (day 46)
How to salvage CAR T failure patients?

69 yo with double expressor DLBCL
Prior therapies: RCHOP x6 (2006), RCHOP x6 + XRT (2012), Cyclophosphamide (10/2018), Axi-Cel

D0 Axi-cel
Pre Axi-Cel, Day -7

Post Axi-Cel D+38

D37 Mosun/TDB

Clinical trial!
Conclusion

CAR T cell therapy is expanding in scope and complexity in treating heme malignancies

Clinical efficacy comes at cost of unique and serious toxicities

Clinical expertise and infrastructure are needed to deliver CAR T safely, effectively, and to regulatory standard

Ongoing effects (clinical trials, preclinical studies) aim to further improve efficacy, reduce toxicities, reduce cost, and expand indications.

Participate clinical trials, support research studies!
Thank you!

Questions???????