CARs vs. BiTE in Acute Lymphoblastic Leukemia: PRO BiTE

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Patient Case

Mr. W is a 59-year-old gentleman with relapsed/ refractory pre-B ALL who presents for possible clinical trial participation: Phase 1: CVP/ Inotuzumab.

At the time of diagnosis, he received a BFM-based regimen.

Cytogenetics demonstrated t(1;7)

His induction course was complicated by sepsis, a peri-rectal abcess requiring surgery, and 2 “mini-strokes”.

Day 28 bone marrow: morphologic CR— but still +minimal residual disease (MRD).
Case, continued

• Given his deconditioned status, he was sent to rehab.

• Post-remission therapy (PRT) was delayed secondary to his performance status.

• Follow-up bone marrow done after his 1\textsuperscript{st} course of PRT demonstrated relapsed/refractory ALL (CD19+, CD22+).

• Current ECOG: 1

• Physical exam: unremarkable except for a Grade 2 peripheral neuropathy.
Case, contd.

- Mr. W is not a candidate for the clinical trial given his peripheral neuropathy.

- Blinatumomab was just FDA approved around this time—so he was started on treatment with this.
Adult ALL:
Novel Approaches Needed

Overall survival at 3 years for 759 adults enrolled on 5 CALGB trials: 1988-2001

- < 30 y (n = 280)
- 30-59 y (n = 350)
- > 60 y (n = 129)
- Overall (n = 759)

Courtesy of Wendy Stock
Adult ALL

• More than 50% of adults with ALL will relapse.

• At the time of relapse, the only KNOWN cure is allogeneic HSCT (AHSCT).

• However, patients typically need to be in remission to be able to proceed to AHSCT.
Blinatumomab (MT103)® A T Cell-Engaging BiTE Antibody

Adapted from: Nagorsen D et al; Blood 2009; 114: 2723
Safety and Activity of Blinatumomab for Adult Patients with Relapsed or Refractory B-precursor acute lymphoblastic leukaemia: a multi-centre single arm Phase 2 study

- 189 pts (Ph chromosome negative)
- Median age 39 years (range 18-79)
- Prior lines of salvage therapy
  - 0: 20%
  - 1: 41%
  - 2: 22%
  - >2: 17%
- Bone marrow blast count
  - < 50%: 31%

## Toxicities

<table>
<thead>
<tr>
<th>Adverse Events (any grade)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>60%</td>
</tr>
<tr>
<td>Headache</td>
<td>34%</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>28%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>26%</td>
</tr>
<tr>
<td>Nausea</td>
<td>24%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>24%</td>
</tr>
<tr>
<td>Constipation</td>
<td>21%</td>
</tr>
<tr>
<td>Anemia*</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Febrile neutropenia, neutropenia, and anemia: most common Gr 3/4 AEs

**3 pts (2%): Gr 3 cytokine release syndrome

***52% of pts had neurologic events: 76% Gr 1 or 2

Blinatumomab: Responses

- Response rate: 43% CR/ CRi
- 40% of responders went on to alloBMT
- MRD response: 82%
- Median RFS: 5.9 months; OS: 6.1 months
- Only significant predictor of response: bone marrow blast count < 50%
- Very encouraging results in a heavily pre-treated group of patients
- December 2014: Blinatumomab FDA approved for relapsed/ refractory Ph neg ALL

TOWER Study

• Phase 3 trial
• 2:1 randomization
• Randomized pts to Blinatumomab or treatment with 1 of the following regimens:
  --FLAG +/-anthracycline
  --high dose cytarabine based
  --high dose methotrexate based
  --clofarabine based
Best Hematologic Response Within 12 Weeks after Treatment Initiation.

Table 2. Best Hematologic Response Within 12 Weeks after Treatment Initiation.*

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Blinatumomab Group (N = 271)</th>
<th>Chemotherapy Group (N = 134)</th>
<th>Treatment Difference (95% CI)</th>
<th>P Value †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>% (95% CI)</td>
<td>no.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Complete remission with full hematologic recovery</td>
<td>91</td>
<td>33.6 (28.0–39.5)</td>
<td>21</td>
<td>15.7 (10.0–23.0)</td>
</tr>
<tr>
<td>Complete remission with full, partial, or incomplete hematologic recovery</td>
<td>119</td>
<td>43.9 (37.9–50.0)</td>
<td>33</td>
<td>24.6 (17.6–32.8)</td>
</tr>
<tr>
<td>Complete remission with partial hematologic recovery</td>
<td>24</td>
<td>8.9 (5.8–12.9)</td>
<td>6</td>
<td>4.5 (1.7–9.5)</td>
</tr>
<tr>
<td>Complete remission with incomplete hematologic recovery</td>
<td>4</td>
<td>1.5 (0.4–3.7)</td>
<td>6</td>
<td>4.5 (1.7–9.5)</td>
</tr>
</tbody>
</table>

* Data are summarized for all patients who underwent randomization (intention-to-treat population). Complete remission was defined as 5% or less bone marrow blasts and no evidence of disease and was further characterized according to the extent of recovery of peripheral blood counts as follows: complete remission with full recovery (platelet count of >100,000 per microliter and absolute neutrophil count of >1000 per microliter), complete remission with partial recovery (platelet count of >50,000 per microliter and absolute neutrophil count of >500 per microliter), or complete remission with incomplete recovery (platelet count of >100,000 per microliter or absolute neutrophil count of >1000 per microliter).

† Rates were compared with the use of a Cochran–Mantel–Haenszel test, with adjustment for the following stratification factors: age (<35 vs. ≥35 years), previous salvage therapy (yes vs. no), and previous allogeneic stem-cell transplantation (yes vs. no).

Efficacy End Points.

A Overall Survival

Median Overall Survival (mo)
- Blinatumomab: 7.7 (95% CI, 5.6–9.6)
- Chemotherapy: 4.0 (95% CI, 2.9–5.3)

Hazard ratio: 0.71 (95% CI, 0.55–0.93)
P = 0.01

B Overall Survival Censored at Time of Stem-Cell Transplantation

Median Overall Survival (mo)
- Blinatumomab: 6.9 (95% CI, 5.3–8.8)
- Chemotherapy: 3.9 (95% CI, 2.8–4.9)

Hazard ratio: 0.66 (95% CI, 0.50–0.88)
P = 0.004

C Event-free Survival

Hazard ratio: 0.55 (95% CI, 0.43–0.73)
P = 0.001

2017;376:836-847
Generation of 19-28z CAR T Cells

1. Construct a CAR
2. Subclone CAR gene into a vector
3. Transduce and expand patient T cells \textit{ex vivo}

Retroviral vector encoding CD19 CAR cDNA

Genetically modified CD19-targeted T cell

Courtesy of Jae Park
### Summary of Clinical Outcomes

**Number of Patients, N=27**

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall CR Rate</td>
<td>24/27 (89%)</td>
</tr>
<tr>
<td>MRD Negative CR Rate</td>
<td>21/24 (88%)</td>
</tr>
<tr>
<td>Median Time to CR (range)</td>
<td>22.5 days (9 – 33)</td>
</tr>
</tbody>
</table>

**Median overall survival:** 8.5 months (this trial)

**Blinatumomab trial:** blina arm: 7.7 months

Jae Park, ASH 2014, Abstract 382
## CRS & Neurological Toxicities

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Severe CRS*</th>
<th>Grade 3/4 Neurotoxicity</th>
<th>Grade 5 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5 (18%)</td>
<td>7 (25%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Pre-T cell Disease Burden</td>
<td>5 (33%)</td>
<td>6 (40%)</td>
<td></td>
</tr>
<tr>
<td>Morphologic disease (n=15)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>MRD (n=13)</td>
<td></td>
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</tr>
</tbody>
</table>

*Requiring vasopressors and/or mechanical ventilation for hypoxia

¶1 patient with ventricular arrhythmia (DNR) and 1 patient had seizure, but unknown cause of death

- No GvHD exacerbation was observed in patients with prior allo-HSCT
- CRS managed with IL-6R inhibitor (3 pts), steroid (2 pts), IL-6R inhibitor+steroid (6 pts)
- Neurological symptoms are reversible, and can occur independent of CRS

Jae Park, ASH 2014, Abstract 382
Cons of CAR T Cells

• Very encouraging response rates. However, most trials in adults preliminary. In ALL—MSK is the main experience to date—so unclear how results will apply on a larger scale in ALL.

• JUNO ALL study in adults closed secondary to neurotoxicity/deaths.

• Toxicity still significant even in MSK trial.

• Unclear of long term effects on the immune system, other complications related to viral integration.
Pros of Blinatumomab

- Larger numbers of patients on an international scale.

- Better long term toxicity data and survival data (data also available in the MRD setting).

- Randomized study showing benefit over standard of care chemotherapy.

- Overall survival not very different from CAR T cells and much fewer toxicities.
Back to our case

- Mr. W achieves a morphologic and cytogenetic remission after 1 cycle of blinatumomab. Molecular testing—MRD by flow—demonstrates evidence of complete molecular remission. He receives 1 more cycle of blinatumomab and then receives a MUD AH SCT.