Outcomes of Patients with Large B-Cell Lymphomas and Progressive Disease Following CD19-Specific CAR T-cell Therapy

Background

CD19-specific CAR T-cell therapy (CART) is effective in patients with relapsed/refractory (R/R) large B-cell lymphomas.

- Durable complete response (CR) rates of ~ 40%

Patients generally do not experience prolonged disease control if they are unable to achieve a CR.

Little data exists on outcomes of patients if they progress following CD19-specific CART.
Methods

We identified patients at our institution who met the following criteria:

1) Developed progressive disease (PD) after CD19-specific CART

2) Did not receive any protocol-specified anti-lymphoma therapy after CART infusion

3) Treated for one of the following histologies:
   - Diffuse large B-cell lymphoma (DLBCL)
   - Transformed follicular lymphoma (tFL)
   - Primary mediastinal B-cell lymphoma (PMBCL)
   - High-grade B-cell lymphoma (HGBCL)
Methods

Primary Analysis: Overall Survival (OS) after PD

Secondary Analyses: OS based on the following characteristics

1) Timing of PD
   - Initial PD – progression on initial disease response assessment
   - Delayed PD – progression on subsequent disease response assessment

2) Use of bridging therapy – any anti-lymphoma therapy given between T-cell collection and CART

3) Ability to receive subsequent therapy after PD
Methods

NOT INCLUDED IN THIS ANALYSIS:

CART product and construct
CART dose
Lymphodepleting chemotherapy regimen
Inflammatory markers
Cytokine release syndrome
Neurotoxicity
Potential mechanism(s) of escape and progression
### Results: Patient Characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>TOTAL (N = 58)</th>
<th>INITIAL PD (N = 30)</th>
<th>DELAYED PD (N = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>60 (26 - 75)</td>
<td>58 (29 - 70)</td>
<td>60.5 (26 - 75)</td>
<td>0.251</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td>0.536</td>
</tr>
<tr>
<td>DLBCL</td>
<td>34 (58.6%)</td>
<td>19 (63.3%)</td>
<td>15 (53.6%)</td>
<td></td>
</tr>
<tr>
<td>HGBCL</td>
<td>12 (20.7%)</td>
<td>4 (13.3%)</td>
<td>8 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>PMBCL</td>
<td>3 (5.2%)</td>
<td>2 (6.7%)</td>
<td>1 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>tFL</td>
<td>9 (15.5%)</td>
<td>5 (16.7%)</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
<td>0.358</td>
</tr>
<tr>
<td>0-1</td>
<td>12 (20.7%)</td>
<td>4 (13.3%)</td>
<td>8 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>37 (63.8%)</td>
<td>21 (70.0%)</td>
<td>16 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>9 (15.5%)</td>
<td>5 (16.7%)</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Median LDH (pre-CART)</td>
<td>210 (111 - 2339)</td>
<td>250 (117 - 2339)</td>
<td>189 (111 - 691)</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Poor OS after progressive disease

Survival Probability

Time After Progression (months)

MEDIAN = 5.3 MONTHS

Strata

Number at risk

58 17 7 4 3 1
Initial PD is associated with inferior survival

P = 0.038

Survival Probability
Time After Progression (months)
Median = 13.42 months
Median = 3.75 months

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed PD, N</td>
<td>28</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Initial PD, N</td>
<td>30</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
## Results: Bridging Therapy

<table>
<thead>
<tr>
<th>Bridging Therapy</th>
<th>TOTAL N = 20 (34.5%)</th>
<th>INITIAL PD N = 12 (40.0%)</th>
<th>DELAYED PD N = 8 (28.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy +/- steroids</td>
<td>9 (45.0%)</td>
<td>4 (33.3%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Intrathecal chemotherapy</td>
<td>1 (5.0%)</td>
<td>0 (0.0%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Novel/targeted agent +/- steroids</td>
<td>5 (25.0%)</td>
<td>4 (33.3%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>5 (25.0%)</td>
<td>4 (33.3%)</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>

**BRIDGING THERAPY:**
Any anti-lymphoma therapy given between T-cell collection and CART
Impact of bridging therapy on survival

P = 0.37

Survival Probability

Time After Progression (months)

NO, N = 38

YES, N = 20

MEDIAN = 3.16 MONTHS

MEDIAN = 7.14 MONTHS

Number at risk

Time After Progression (months)

Bridging Therapy

38

20

13

4

5

2

6

2

3

1

3

1

2

1

0

0

1
Impact of bridging therapy and type of progression on survival

**Survival Probability**

<table>
<thead>
<tr>
<th>Time After Progression (months)</th>
<th>No Bridging + Delayed PD</th>
<th>No Bridging + Initial PD</th>
<th>Bridging + Delayed PD</th>
<th>Bridging + Initial PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>20</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>30</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>40</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**MEDIAN OS (MONTHS)**
- No Bridging + Delayed PD: 13.55
- No Bridging + Initial PD: 5.20
- Bridging + Delayed PD: 3.19
- Bridging + Initial PD: 2.34

**P = 0.19**
Impact of bridging therapy and type of progression on survival

**Survival Probability**

- No Bridging + Delayed PD, $N = 20$
  - Median = 13.55 months
- Other N = 38
  - Median = 3.55 months

**Number at risk**

<table>
<thead>
<tr>
<th>Time After Progression (months)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>20</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>38</td>
<td>38</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

$P = 0.059$
Next treatment after progression

<table>
<thead>
<tr>
<th>INITIAL SUBSEQUENT THERAPY</th>
<th>TOTAL (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T-CELL</td>
<td>14</td>
</tr>
<tr>
<td>NOVEL THERAPY</td>
<td>13</td>
</tr>
<tr>
<td>CHEMOTHERAPY +/- R</td>
<td>7</td>
</tr>
<tr>
<td>ANTI-PD1 INHIBITOR</td>
<td>4</td>
</tr>
<tr>
<td>RADIOTHERAPY</td>
<td>4</td>
</tr>
<tr>
<td>INTRATHECAL</td>
<td>1</td>
</tr>
<tr>
<td>ALLOGENEIC HSCT</td>
<td>1</td>
</tr>
</tbody>
</table>

44 (76%) patients received ≥ 1 subsequent therapies after PD.

 Patients receiving ≥ 1 subsequent therapies after PD had a lower risk of death, compared to those who did not.
  • HR 0.48, 95% CI 0.234-0.99, P = 0.0476

6 (10%) patients enrolled onto a clinical trial as next line therapy.

5 (9%) patients eventually received an allogeneic HSCT, 2 of whom are still alive.
Conclusions

Patients with PD following CD19-specific CART have poor outcomes.

Patients with initial PD had inferior overall survival.

More effective strategies are needed to improve CR rates and prevent PD.

Planning for the potential of PD following CART should figure into the treatment algorithm for R/R disease.

These data set the stage for novel combinations in the future (eg bridging therapy, maintenance therapy).

These data should inform clinical trial design.
Acknowledgments

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