Are CAR T-Cells the Solution for Chemotherapy Refractory Diffuse Large B-Cell Lymphoma?

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Disclosure(s)

I do not intend to discuss an off-label use of a product during this activity

I currently have or have had the following relevant financial relations to disclose:

• Research grant from KITE Pharma to study the outcome of chemotherapy refractory diffuse large B-cell Lymphoma.
Relapsed / Refractory Diffuse Large B cell Lymphoma

- DLBCL accounts for ~30-35% of Non Hodgkin Lymphoma
- In United States, the reported annual incidence of new DLBCL is ~ 25,000
- Despite significant progress with addition to Rituximab to CHOP chemotherapy, at least one third of patients will have either relapsed and refractory DLBCL
Subtypes of DLBCL at higher risk of treatment failure

• IPI score is the most widely used prognostic tool to identify high risk DLBCL

• It remains valid in the Rituximab era

• Since, even in high risk IPI, the EFS is above 50%, it does not identify those with particularly worst outcome
“Double Hit”

• Concurrently present MYC and BCL-2 gene rearrangements are referred to as so called double hit (~5% of DLBCL)

• BCCA reported inferior 5 year survival for DLBCL with MYC translocation when treated with R-CHOP

• MYC gene rearrangement also associate with increased risk of CNS relapse
“Dual Expresser”

- Concurrent over-expression of MYC (>40%) and BCL-2 (>50%) is found in ~25% of the patients with DLBCL.

- A BCCA cohort of patients treated with R-CHOP showed inferior outcome associated with dual expression of MYC and BCL-2.
DLBCL subtypes ABC vs GCB

- Lenz et al using gene expression profile evaluated a cohort of DLBCL patients treated with R-CHOP

- Patients with ABC subtype had inferior progression free and overall survival
Prognosis of relapsed and refractory DLBCL

• Despite the progress with addition of Rituximab, ~10-15% have primary refractory disease
• Additionally, ~25% of patient with DLBCL will relapse after achieving CR
• Patient with chemotherapy refractory or those with early relapse carry a particularly worse prognosis
CORAL study - ABC vs GCB

• CORAL study compared R-ICE vs. R-DHAP as salvage regimen for relapsed and refractory DLBCL

• It showed similar response rate after 3 cycles of R-ICE (63.5%) and R-DHAP (62.8%)

• Further analysis showed GCB-like DLBCL was associated with better PFS in DHAP arm
Coral Study – Presence or Absence of MYC rearrangement

• In CORAL study 17% had MYC gene rearrangement
• Presence of MYC (MYC+) was associated with worse outcome
  – 4 year PFS 18% vs 42%
  – 4 year OS 29% vs 62%
CORAL study

- DLBCL with refractory to first line chemotherapy or relapse < 12 months after the diagnosis had a response rate of 46% vs 88%

- If relapse >12 months from diagnosis, the prior exposure to Rituximab did not affect the outcome

Failure from diagnosis was <12 months
Outcome of DLBCL patients who did not respond to salvage chemotherapy in CORAL study

- 145 patients failed R-DHAP or R-ICE
- Median age 56 years (range 20-67, 31% > 60y)
- IPI score
  - 0-1 in 30%
  - 2-3 in 56%
  - 4-5 in 14%
Outcome of DLBCL patients who did not respond to salvage chemotherapy in CORAL study

- 3\textsuperscript{rd} line therapies were as follows:
  - ICE type – 19% → CR 23% and PR 23%
  - DHAP type – 19% → CR 35% and PR 8%
  - Gemcitabine based – 16% → CR 9% and PR 4%
  - CHOP like – 8% → CR 25% and PR 25%
  - Dexa BEAM – 8%
  - Other with or without rituximab - 31%

- ORR to 3\textsuperscript{rd} line chemotherapy → 43%
  - CR – 21%
  - CR\textsubscript{u} – 8%
  - PR – 14%

- So, out of 145 patients, 64 (44%) underwent transplant
Outcome of DLBCL patients who did not respond to salvage chemotherapy in CORAL study

• Median OS after failure of 2\textsuperscript{nd} line therapy was 5.9 months and was not influenced by the type of 3\textsuperscript{rd} line therapy

• Following 3\textsuperscript{rd} line therapy, the OS in patients achieving
  • CR/CRu 63.6 months (1 year OS of 72.1%)
  • PR 12.8 months (1 year OS 41.6%)
  • No response 4.4 months (1 year OS 9.2%)

• Median OS
  – Transplanted 11.1 months
  – Not transplant – 5 months
Outcome of Pts with chemotherapy refractory and early progressive DLBCL after R-CHOP

- BCCA reviewed 1126 patients with DLBCL between 2000 to 2009
- 166 patients (15%) had primary refractory or early relapsing disease
- Out of these 166 pts, 93 were older than 70 y and too frail to receive > 2 cycles of R-CHOP
- The remaining 73 pts, 33 (45%) had primary refractory lymphoma and 40 (55%) relapsed within 3 months of achieving a CR/PR
Outcome of Pts with chemotherapy refractory and early progressive DLBCL after R-CHOP

- Of these 73 patients, only 37 (50%) were eligible for treatment with curative therapy with multiagent salvage regimen
- Only 10 patients were able to undergo autoHCT
- Median OS of these 73 patients was 10 months
- Only 6 patients were alive without evidence of disease
  - 5 early relapse and 1 primary refractory
  - 3 of these without ASCT and 3 with ASCT
Retrospective study by Cornell on outcome of DLBCL refractory to second line chemotherapy

- 108 patients with relapsed and refractory DLBCL between 1996 and 2007
- Records available only on 74 patients for analysis
- Second-line chemotherapy: 47 patients responded and 27 patients were non-responders
- Response rate in primary refractory was 29% (5 of 17) and in relapsed disease it was 74% (42 of 57 pts)
Retrospective study by Cornell on outcome of DLBCL refractory to second line chemotherapy

- Out of 27 non-responder patients, 21 patients received chemotherapy and only 15 received combination intensive chemotherapy
- Only 5 patients responded to third line treatment which was chemotherapy
- Out 5 only 3 patients underwent autoHCT and only 1 patient experience extended remission
- Median OS was only 4 months in the non-responders from the time of second line chemotherapy
- And only 1 patient (4%) was alive at one year
Post ASCT relapsed DLBCL

• A retrospective study of 56 patients with relapsed or refractory DLBCL post ASCT was reported
• The median OS from progression following ASCT for the cohort was 9.9 months
• Patients who progressed less than 1 year from ASCT had a significantly shorter OS than those who progressed at 1 year or greater from ASCT (8.2 vs. 26.7 months)
• Patients with at least stable disease following ASCT had a longer OS than those who progressed immediately after ASCT (12.3 vs. 5.3 months, P50.01)
# AlloHCT in DLBCL

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Median age, years (range)</th>
<th>Prior auto-HCT (%)</th>
<th>Rituximab prior to allo-HCT (%)</th>
<th>Donor type</th>
<th>Conditioning</th>
<th>NRM/ TRM (%) (years)</th>
<th>Relapse (%) (years)</th>
<th>OS (%)</th>
<th>PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rezvani et al.¹</td>
<td>32</td>
<td>52 (18–67)</td>
<td>75</td>
<td>NA</td>
<td>72</td>
<td>MRD, 66%/URD, 34%</td>
<td>NMAC: Flu+TBI 2 Gy (91%)</td>
<td>25 (3)</td>
<td>41 (3)</td>
<td>45 (3)</td>
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<tr>
<td>Thomson et al.²</td>
<td>48</td>
<td>46 (23–64)</td>
<td></td>
<td>56</td>
<td>17</td>
<td>MRD, 62%/URD, 38%</td>
<td>RIC: Flu+MEL+Alemtuzumab</td>
<td>32 (4)</td>
<td>33 (4)</td>
<td>47 (4)</td>
</tr>
<tr>
<td>Servent et al.³</td>
<td>68</td>
<td>48 (17–66)</td>
<td>79 (incl. allo-HCT)</td>
<td>40</td>
<td>19</td>
<td>MRD, 62%/URD, 18%</td>
<td>NMAC: Flu+TBI 2 Gy (76%)</td>
<td>23 (1)</td>
<td>41 (2)</td>
<td>49 (2)</td>
</tr>
<tr>
<td>Lazarus et al.⁴</td>
<td>79</td>
<td>46 (21–59)</td>
<td>0</td>
<td>NA</td>
<td>42</td>
<td>MRD, 100%</td>
<td>MAC: CY+TBI (12 Gy)+/BU (82%)</td>
<td>45 (5)</td>
<td>33 (5)</td>
<td>22 (5)</td>
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<td>van Kampen et al.⁴</td>
<td>101</td>
<td>46 (18–66)</td>
<td>100</td>
<td>19</td>
<td>26</td>
<td>MRD, 71%/URD, 29%</td>
<td>MAC: CY+TBI (12 Gy)+/Bu (67%)</td>
<td>28 (3)</td>
<td>30 (3)</td>
<td>52 (3)</td>
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<tr>
<td>Rigacci et al.⁵</td>
<td>165</td>
<td>43 (16–65)</td>
<td>100</td>
<td>NA</td>
<td>33</td>
<td>MRD, 65%/URD, 35%</td>
<td>MAC 30%: TBI-based RIC (70%): Flu-based</td>
<td>28 (3)</td>
<td>25 (3)</td>
<td>39 (5)</td>
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<tr>
<td>Bacher et al.²</td>
<td>396</td>
<td>48 (18–69)</td>
<td>32</td>
<td>67</td>
<td>36</td>
<td>MRD, 33%/URD, 67%</td>
<td>MAC: CY+TBI (12 Gy)+/BU (77%)</td>
<td>56 (5)</td>
<td>26 (5)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

Abbreviations: allo-HCT = allogeneic cell transplantation; auto-HCT = autologous hematopoietic cell transplantation; Eto = etoposide; Flu = fludarabine; MAC = myeloablative conditioning; MEL = melphalan; MRD = matched related donor; N = number of patients; NA = not available; NMAC = non-myeloablative conditioning; NRM = non-relapsed mortality; PD = progressive disease; RIC = reduced-intensity conditioning; SD = stable disease; Thio = thiotepa; TRM = treatment-related mortality; URD = unrelated donor.
CAR T-cells

• Chimeric antigen receptor T-cells (CAR T-cells) are genetically engineered T-cells that can engage target via single chain variable fragment (scFv) derived from an antibody

• T cells expressing anti-CD19 CARs recognize and kill CD19 target cells

• NCI reported CR in chemotherapy-refractory DLBCL after receiving anti-CD19 CAR T cells.
Generation of CARs typically refer to the intracellular signaling domains

- 1\textsuperscript{st} generation CARs include only CD3ζ

- 2\textsuperscript{nd} generation CARs include a single costimulatory domain derived from either CD28 or 4-1BB

- 3\textsuperscript{rd} generation CARs include two costimulatory domains, such as CD28, 4-1BB, and other costimulatory molecules
Preparation of Anti-CD19 CAR T Cells

- scFv region that recognizes CD19 was derived from FMC63 monoclonal antibody
- CAR contained CD28 costimulatory domain and T-cell receptor (TCR) – T-cell activation domain

Anti-CD19 CAR T cells were produced by
- activating peripheral-blood mononuclear cells (PBMCs) with anti-CD3 antibody OKT3 on day 0
- Transducing T cells on day 2 gammaretroviral vector encoding the CAR
- Cells were ready for infusion on day 10
CAR vector construct

Viral vector

Target binding domain: antibody derived [scFv]

Hinge

Transmembrane domain

Costimulatory domain: CD28

Essential activating domain: CD3ζ

CAR-engineered T cell

Cytolytic activity

Cytokine release

Proliferation

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Anti-CD19 CAR Treatment Plan

• The clinical treatment plan consisted of a course of chemotherapy, followed 1 day later by a single infusion of anti-CD19 CAR T cells.

• The chemotherapy was cyclophosphamide at a total dose of either 120 or 60 mg/kg (Table 1), followed by five daily doses of fludarabine 25 mg/m2.

• Chemotherapy was administered before anti-CD19 CART cells to deplete endogenous leukocytes that can inhibit the antimalignancy activity of adoptively transferred T cells.
Response to CAR T-cells

- Of the seven evaluable patients with DLBCL, four obtained CRs, two obtained PRs, and one had stable disease (SD) after infusion of CAR T cells.
  - (A) CR of chemotherapy refractory primary mediastinal B-cell lymphoma (PMBCL)
  - (B) CR of lymphoma in chemotherapy refractory PMBCL with extensive liver involvement.
  - (C) CR of diffuse large B-cell lymphoma, not otherwise specified, who had extensive splenic lymphoma.
Toxicities of CAR T-cell therapy

- The most troublesome toxicities experienced by patients on this protocol were hypotension and neurologic toxicities
- Importantly, all patients recovered completely from their neurologic toxicities.
- Two patients with severe toxicities by infusing the IL-6 receptor–blocking antibody tocilizumab. One of the patients had hypotension, and the other had predominantly neurologic toxicity; the toxicity did not substantially improve in either patient.
Thank you