CAR T Cell Therapy

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Contents

- What is CAR T cell therapy and how does it work?
- CAR T cell trials and approved therapies in hematological malignancies;
- Treatment approaches in Multiple Myeloma;
- CAR T cell therapies targeting BCMA in Multiple Myeloma;
CAR T Cell Therapy

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Chimeric Antigen Receptor (CAR) T Cell Therapy

- Adoptive cell therapy that utilizes autologous T cells engineered to express CARs
CARs consist of extracellular antigen binding domain, a transmembrane domain, and an intracellular activation domain.
Advantages and Drawbacks of CAR T Cell Therapy

**ADVANTAGES**
- Target specificity
- Lower potential for graft versus host disease
- “Living drug”
- Immunotherapy/gene therapy

**DRAWBACKS**
- Cytokine release syndrome (CRS)/neurotoxicity
- Relapse (hard to predict)
- Individualized manufacturing process
- Complicated chain of cost/chain of identity; logistics issue
- Cost
Current Landscape of CAR T Cell Therapy

- Over 400 clinical CAR T cell therapy trials registered on ClinicalTrials.gov
  - ~150 in the US; ~190 in China
  - China is a dominant player in the field
- Majority of CAR T cell trials are for hematologic malignancies
  - ~75% of registered CAR T clinical studies
  - 2 FDA-approved CAR T cell therapies
- CAR T cell approaches for solid tumors, autoimmune disease, and infectious disease are also in development
  - e.g., EGFRvIII for glioblastoma; HER2 for breast cancer; mesothelin for ovarian cancer, NKG2DL for gastric cancer, CD4 for HIV

www.ClinicalTrials.gov
CAR T Cell Therapy

- What is CAR T cell therapy and how does it work?
- CAR T cell trials and approved therapies in hematological malignancies;
- Treatment approaches in Multiple Myeloma;
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General Study Design of a CAR T Cell Trial

Screening & Enrollment → Leukapheresis → Preconditioning Chemotherapy\(^a\) → CAR T Cell Infusion → First Response Assessment

Manufacturing (No Bridging Therapy Allowed) → Investigational Product Hospitalization Period → Follow-up Post-treatment and Assessment

\(^a\) cyclophosphamide; fludarabine; cyclophosphamide + fludarabine
First FDA-approved CAR T cell therapy - KYMRIAH®
  - CD19 CAR T cells
  - Approved for acute lymphoblastic leukemia (ALL)\textsuperscript{a} and diffuse large B-cell lymphoma (DLBCL)\textsuperscript{b}

- ORR = 81% (ALL) and 50% (DLBCL)\textsuperscript{b}
- Median EFS/PFS = not reached (ALL)\textsuperscript{a} and 3.2 months (PFS for DLBCL)\textsuperscript{b}
- Median OS = 19.1 months (ALL)\textsuperscript{a} and 22.2 months (DLBCL)\textsuperscript{b}

\textsuperscript{a}Maude et al. 2018 NEJM; 378(5): 439-48
\textsuperscript{b}Schuster et al. 2017 NEJM; 377(26): 2545-54

\textbf{EFS=}	extit{event-free survival; ORR=}	extit{overall response rate; OS=}	extit{overall survival; PFS=}	extit{progression-free survival}
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma


- 2nd FDA-approved CD19 CAR T cell therapy - YESCARTA®
  - Approved for R/R DLBCL, DLBCL arising from FL, PMBCL, high-grade B-cell lymphoma
- ORR = 82%
- Median PFS = 5.8 months
- Median OS = not reached

Neelapu et al. 2017 NEJM; 377(26): 2531-44

FL=follicular lymphoma; R/R=relapsed/refractory; PMBCL=primary mediastinal large B-cell lymphoma
# Safety Summary of FDA-Approved CAR T Cell Therapies

<table>
<thead>
<tr>
<th></th>
<th>Kymriah® (ALL)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Kymriah® (DLBCL)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yescarta® (DLBCL)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade ≥3</td>
<td>All Grade</td>
</tr>
<tr>
<td>CRS</td>
<td>79%</td>
<td>49%</td>
<td>74%</td>
</tr>
<tr>
<td>Neurologic toxicities</td>
<td>72%</td>
<td>21%</td>
<td>58%</td>
</tr>
<tr>
<td>Prolonged cytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>-</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>-</td>
<td>40%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>27%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Kymria USPI; <sup>b</sup>Yescarta USPI; <sup>c</sup>Not resolved by Day 28; <sup>d</sup>Not resolved by Day 30
Other Hematologic CAR T Cell Targets

- CD20 for ALL, DLBCL, mantle cell lymphoma, FL, Non-Hodgkin lymphoma (NHL)
- CD22 for ALL, NHL, chronic lymphocytic leukemia, FL
- CD30 for Hodgkin lymphoma, anaplastic large cell lymphoma
- CD123 for acute myeloid leukemia
- CD138 for multiple myeloma (MM)
- **B-cell maturation antigen (BCMA)** for MM
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Multiple Myeloma

- Serious cancer of the bone marrow

- Incidence per year
  - US: 6.1 per 100,000\textsuperscript{a}
  - Europe: 4.5–6.0 per 100,000\textsuperscript{b}
  - China: 0.6 per 100,000\textsuperscript{c}

- Incurable disease
  - First-line therapy will eventually encounter disease resistance leading to disease progression
  - 5-year survival rate <50%
  - High unmet medical need

\textsuperscript{a}Costa 2017 Blood Adv; 1(4): 282-7; \textsuperscript{b}Palumbo 2011 Blood; 118: 4519-39; \textsuperscript{c}Ferlay 2012 GLOBOCAN 2012
**ESMO Guidelines for MM**

- **Indolent MM**: Immediate treatment not recommended
- **<70 years**: Induction followed by high-dose therapy with ASCT as standard therapy
- **Elderly**: Bortezomib/melphalan/prednisone (VMP) or lenalidomide + low dose dexamethasone (Rd)
- **R/R MM**: Proteasome inhibitor- or lenalidomide-containing regimens
- **Advanced Cases**: Pomalidomide + low-dose dexamethasone and daratumumab

Moreau et al. 2017 *Ann Oncol*; 28(suppl 4): iv52-61
In Asia, ESMO and NCCN guidelines are used to guide treatment.

However, new drugs for patients with MM are not always available (e.g., anti-CD38 antibody not marketed in China)

High medical expenditures are often not covered by health insurance and patients cannot afford to cover costs.

Differences in dosage and treatment effects in Asian and Western populations; treatments require further optimization for Asian patients.

New treatments developed independently in China, such as CAR T cell therapy, offer a more affordable and more accessible treatment option for patients in Asia.
CAR T Cell Therapy

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- CAR T cell trials and approved therapies in hematological malignancies;
- Treatment approaches in Multiple Myeloma;
- CAR T cell therapies targeting BCMA in Multiple Myeloma;
Many targets available for MM:
- Integrin β7, CD70, CD38, CD138, CD19, κ light chain, SLAMF7, and BCMA

BCMA is an attractive target for MM
- Member of the tumor necrosis factor family
- BCMA expressed exclusively in B-cell lineages
- Involved in B-cell maturation and differentiation
- Widely expressed in malignant plasma cells

BCMA-targeted CAR T cells are furthest in development
- BCMA CAR T – National Cancer Institute (NCI)
- bb2121 – bluebird bio
- LCAR-B38M – Nanjing Legend Biotech
Phase 1 study of 24 patients with R/R MM
- Results from 16 patients treated at highest dose
  - ORR = 81%
  - 94% of patients had decrease in myeloma marker
  - CRS = 94%
  - Neurotoxicity = confusion and delirium

NCI BCMA CAR T

Brudno et al. 2018 JCO; 36(22): 2267-80

scFV=single chain variable fragment
Phase 1 study in 43 patients with R/R MM

- ORR = 95.5% for 22 patients treated with >150x10^6 CAR+ T cells
- Median PFS = 11.8 months for 18 patients treated with 150-800x10^6 CAR+ T cells
- CRS = 63%
- Neurotoxicity = 33%

Raje et al. 2018 JCO; 36(suppl): abstr 8007
LCAR-B38M

Llama dual-epitope binding VHH

4-1BB

CD3ζ

Other CAR T players

LCAR-B38M VHH Dual-Epitope Binding CAR
Phase 1 study in 35 patients with R/R MM

Patients treated before April 5, 2017

<table>
<thead>
<tr>
<th>Best response</th>
<th>Total</th>
<th>PR</th>
<th>VGPR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>100%</td>
<td>6.7%</td>
<td>30%</td>
<td>63.3%</td>
</tr>
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</table>

VGPR=very good partial response; sCR=stringent complete response

Fan et al. 2017 JCO; 35(suppl): LBA3001
- CRS = mostly grade 1-2
- Neurotoxicity = none
- B-cell aplasia = recoverable

Cytokine Release Syndrome

<table>
<thead>
<tr>
<th>CRS Free</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5 (Death)</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>17</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fan et al. 2017 JCO; 35(suppl): LBA3001
LCAR-B38M – Clinical Efficacy

Before CAR T Cell Treatment

Day 19

Day 84

Fan et al. 2017 JCO; 35(suppl): LBA3001
Subject#23

2017.2.1 Before CAR T Cell Treatment

2017.4.19

2017.8.23

LCAR-B38M – Clinical Efficacy
Cytokine Profile

Fan et al. 2017 JCO; 35(suppl): LBA3001
57 patients with R/R MM have been treated with LCAR-B38M in our institution
   – Updated results will be presented at ASH 2018

US Phase Ib/II study is ongoing and China Phase II study is planned
Future Directions for CAR T Cell Therapy

- Allogenic CAR T cell therapy
  - Universal, “off the shelf” CAR T cells

- Fourth generation CAR T constructs
  - Inducible expression of cytokines (e.g. IL-12) within the tumor microenvironment

- CRISPR gene editing technology
  - Specific, directed insertion of CAR gene to T cell genome

- Combination with other therapy
  - CAR T + stem cell transplant (SCT bridging)
  - CAR T + targeted therapy

References:
- Qasim et al. 2017 Sci Transl Med; 9(374); Zhang et al. 2011 Mol Ther; 19(4): 751-9
- Ren et al. 2017 Oncotarget; 8: 17002-11; Maude et al. 2017 JCO; 35(suppl): 103
- Chong et al. 2017 Blood; 129: 1039-41
CAR T cell therapy is an immunotherapy that utilizes patients’ own engineered T cells to attack cancer cells.

Promising, possibly curative treatment for some hematologic malignancies:
- 2 FDA approved therapies (KYMRIAH® and YESCARTA®) for ALL and DLBCL
- BCMA-targeted CAR T therapies for MM show encouraging results

Future of CAR T therapy:
- New generations of CAR constructs
- More specific targets for broader range of indications
- Improved manufacturing/allogenic options and universal CAR T cells
- More safety management choices
Acknowledgments

The Second Affiliated Hospital of Xi’an Jiaotong University

Nanjing Legend Biotech Co.