Chimeric Antigen Receptor T-Cell Therapy in Hematologic Malignancies

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DISCLOSURES

• Conflict of Interests:
  Precision Biosciences; Mustang Therapeutics

• Discussion of off-label drug use:
  Tocilizumab
Presentation Objectives

• Overview of chimeric antigen receptor (CAR) T structure, mechanism of action, and production
• Summary of relevant CAR T trials in the US
• CAR T related Toxicities and management
• Patient screening
• CAR T optimization
CAR T-cell Design

First generation

Second generation

Third generation

Antigen-recognition domain

Signalling domains

Jackson, H. J. et al. (2016) Driving CAR T-cells forward
Advantages of CARs

- Highly specific: targets could be TAA, ligand, etc
- HLA-independent target recognition
- Living drug: in vivo expansion and multiple rounds of killing
- Travel to places that antibodies can not
- The potential to generate long-term antitumor immunity
- Minimal risks of GVHD
CAR T Cell Therapy

Ex vivo cell engineering and processing

PBMC collection

T cell activation

CAR delivery

Lymphodepletion
Not all CD19CARs Are Created Equal

(MSKCC) JCAR-015

NCI KTE

COH

UPENN, Navatis

FHCRC/SCH JCAR017

Other variables:
the starting population, manufacturing process, infused products (i.e. defined populations)
The Type of CAR T Cell Matters

Key Variables
1. CAR Structure
2. Manufacture Platform
3. Conditioning regimen

CAR T Trials Worldwide (N=373)

North America: 183
US: 166
East Asia: 105
Europe: 71
CD19CAR T Trials in US
### CD19CAR T Induced High CR Rates B-ALL Trials in Single Academic Centers

<table>
<thead>
<tr>
<th>Study N</th>
<th>Age, yrs</th>
<th>Dose/RP2D</th>
<th>CR,% MRD-CR</th>
<th>Relapse post MRD-CR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC 36</td>
<td>39 (20-73) 33%</td>
<td>0.2-20M/kg</td>
<td>100% 94\textsuperscript{ITT}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SCH 45 (45)</td>
<td>12 (1-27) 62%</td>
<td>0.5-10M/kg 1M/kg</td>
<td>NA 89\textsuperscript{ITT}</td>
<td>47%</td>
<td>EFS 50.8% at 12 months</td>
</tr>
<tr>
<td>CHOP 59</td>
<td>Lentivirus -41BB</td>
<td>82</td>
<td>40% at 12 mo</td>
<td>RFS 45% at 12 mo</td>
<td></td>
</tr>
<tr>
<td>NCIped 55 (52)</td>
<td>13 (4-30) 19%</td>
<td>1-3M/kg 1M/kg</td>
<td>62\textsuperscript{ITT} 55</td>
<td>75% -&gt; HSCT 28% relapsed +HSCT, 2/21 - HSCT, 6/7</td>
<td>28% OS; 56% LFS for MRD-CR median f/u of 2.2 yrs</td>
</tr>
<tr>
<td>MSKCC 51(50)</td>
<td>40 (22-74) 35%</td>
<td>1-3M/kg 1M/kg</td>
<td>82 61</td>
<td>39% -&gt; HSCT 45% relapsed</td>
<td>≥12 Months</td>
</tr>
</tbody>
</table>

5. Park J et al. ASCO 2016

*HSCT TRM 24% (N = 5)*
ELIANA: Study Design

- International, multicenter, open-label, single-arm phase 2 study

Pts (N = 81) aged 3-21 yrs
≥ 5% BM lymphoblasts;
no isolated extramedullary
disease,
no prior CD19-directed
treatment,
no prior gene therapy

- Primary endpoint:
ORR (CR + CRi) within 3 mos; 4-wk maintenance of remission
required

- Secondary endpoints
MRD status, DoR, OS, cellular kinetics, safety


Slide credit: clinicaloptions.com
CD19CAR T Induced High CR Rates in B-ALL Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age, yrs</th>
<th>Dose/ RP2D</th>
<th>CR,% MRD-</th>
<th>Relapse post MRD-CR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC 30</td>
<td></td>
<td>0.2-20M/kg</td>
<td>NA 91\text{ITT}</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SCH 45(43)</td>
<td>1-27</td>
<td>0.5-10M/kg 1M/kg</td>
<td>NA 89\text{ITT}</td>
<td>47%</td>
<td>EFS 51% at 12 mos</td>
</tr>
<tr>
<td>CHOP 59</td>
<td></td>
<td>Lentivirus /-41BB</td>
<td>82</td>
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<tr>
<td>NCIped 55(52)</td>
<td>4-30</td>
<td>1-3M/kg 1M/kg</td>
<td>62\text{ITT} 55</td>
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<td>28% OS; 56% LFS for MRD-CR median f/u of 2.2 yrs</td>
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<tr>
<td>MSKCC 51(50)</td>
<td>22-74</td>
<td>1-3M/kg 1M/kg</td>
<td>82</td>
<td>39% -&gt; HSCT 45% relapsed</td>
<td>27% MRD-CR DFS ≥12 Months</td>
</tr>
<tr>
<td>ELIANA 82(62)</td>
<td>3-23</td>
<td>2-5M/kg or 100M if &gt;50kg</td>
<td>82% 82%</td>
<td>38% at 6 mos 82% N=50</td>
<td>89% OS at 6 mos</td>
</tr>
</tbody>
</table>
## CD19CAR T Trial Toxicities

<table>
<thead>
<tr>
<th>Study</th>
<th>sCRS ≥ gr3</th>
<th>NT≥ gr3</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHCRC</td>
<td>11% (3 grade 5)</td>
<td>39%</td>
<td>N = 3</td>
</tr>
<tr>
<td>SCH N = 45</td>
<td>1 LV dysfunction</td>
<td>5 encephalopathy 3 seizure 1 hydrocephalus</td>
<td>0</td>
</tr>
<tr>
<td>NIH ped</td>
<td>10% grade 3 4% grade 4</td>
<td>No gr4, 13/46 1 HA, 1 dysphasia, 1 delirium</td>
<td>0</td>
</tr>
<tr>
<td>MSKCC</td>
<td>27% 2 (1 arrhythmia; 1 seizure)</td>
<td>29%</td>
<td>N = 3 2 sepsis/MOF 1 seizure</td>
</tr>
<tr>
<td>ELIANA N=62</td>
<td>21% grade 3 27% grade 4</td>
<td>15% (transient) grade 3; no grade 4</td>
<td>N = 2 1 PD (ALL) 1 ICH</td>
</tr>
</tbody>
</table>
CD19CAR T: Impact on CNS Disease

CTL019 (UPENN): (Rheingold et al. ASH 2015)

**Patient population and design:**
53 pediatric ALL patients, 12 with CNS3 relapse
CNS1 or CNS 2 disease at the time of T cell infusion
LP at day 28, 3, 6, 9, & 12 months.

**Results:**
- d-1, 4 pts with CNS 2
- D28, all 4 became CNS1; no pt with CNS relapse
  - CSF from 46/47 (98%) treated patients had detectable CAR by PCR
- 12 months, 9/9 patients in CR at 1 year have CTL019 in CSF
- no CNS relapse in all 53 patients regardless of prior CNS history,
- Neurologic oxicity:
  - Encephalopathy: not increased,
    - 25% in the 12 pts vs 29% (12/41) pt with no prior CNS dz.
  - Seizure: grade 2 to 4 in 4 pts; only one with prior CNS disease and a h/o seizure

A cohort of patients with CNS3 disease at the time of infusion is enrolling.
# CD19CAR T Cell NHL Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ORR N, %</th>
<th>CR</th>
<th>Lymphodepletion</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPenn&lt;sup&gt;1&lt;/sup&gt;</td>
<td>15</td>
<td>47%</td>
<td>40%</td>
<td>any</td>
<td>DLBCL</td>
</tr>
<tr>
<td>UPenn&lt;sup&gt;1&lt;/sup&gt;</td>
<td>13</td>
<td>69%</td>
<td>n/a</td>
<td>any</td>
<td>FL</td>
</tr>
<tr>
<td>FHCRC&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12</td>
<td>50%</td>
<td>8%</td>
<td>Non-Cy/Flu</td>
<td>NHL</td>
</tr>
<tr>
<td>FHCRC&lt;sup&gt;2&lt;/sup&gt;</td>
<td>18</td>
<td>72%</td>
<td>50%</td>
<td>Cy/Flu</td>
<td>NHL</td>
</tr>
<tr>
<td>NCI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>21</td>
<td>86%</td>
<td>52%</td>
<td>Flu/Cy (300mg/kg x 3)</td>
<td>DLBCL, FL</td>
</tr>
<tr>
<td>NCI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>13</td>
<td>62%</td>
<td>23%</td>
<td>Flu/Cy (60-120mg/kg x 1)</td>
<td>DLBCL, FL</td>
</tr>
<tr>
<td>ZUMA-&lt;sup&gt;1&lt;/sup&gt;&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7</td>
<td>71%</td>
<td>51%</td>
<td>Flu/Cy</td>
<td>DLBCL</td>
</tr>
</tbody>
</table>

1. Schuster et al. ASH 2015;
2. Turtle, C et al. ASH 2015;
4. Locke F et al. ASH 2015
CD19 CAR T Multicenter Clinical Trials

- **ALL**
  1. ZUMA-3 adult ALL (KTEC19, Kite Pharma, Phase 1/2)
  2. ZUMA-4 ped ALL (KTEC19, Kite Pharma, phase 1/2)
  3. ELIANA ped ALL (Novatis, Phase2)
  4. ROCKET adult ALL (Juno Therapeutics, phase 2)

- **NHL**
  1. ZUMA-1: refractory DLBCL (KTEC19, phase 1/2)
  2. ZUMA-2: refractory MCL (KTEC19, phase 1/2)
  3. ZUMA-6: refractory DLBCL (KTEC19+ PDL1, phase 1/2)
  3. JCAR017: r/r NHL (JCAR017, phase 1)
  4. JULIET: recurrent DLBCL (CTL0109, phase 2)
ZUMA-1: Multicenter Trial of KTE-C19 in Refractory Aggressive NHL (NCT02348216)

Phase 1

- Refractory DLBCL/PMBCL/TFL
  - N=6

Key inclusion criteria
- Aggressive NHL (DLBCL, PMBCL, or TFL)
- ECOG PS ≤ 1
- No response to previous chemotherapy or relapsed within 12 mos of ASCT
- Prior tx: anthracycline and anti-CD20 mAb

Treatment
- Leukopheresis
- Lymphodepletion: Flu (30mg/m²)+Cy(500mg/m²) x 3
- KTE-C19: 1-2x 10⁶/kg

Phase 2

- Cohort 1
  - Refractory DLBCL
  - N=72
- Cohort 2
  - Refractory PMBCL/TFL
  - N=20

• Primary endpoint
  - Phase 2: ORR (historical control assumption of 20%)

• Key secondary endpoints
  - DOR, OS, Safety, levels of CAR T and Cytokines
ZUMA-1: Responses at 1 and 6 Mos of Follow-up

<table>
<thead>
<tr>
<th>Response %</th>
<th>Phase 1 Combined (n = 7)</th>
<th>Phase 2 PMBCL/TFL (n = 24)</th>
<th>Combined (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DLBCL (n = 77)</td>
<td>DLBCL (n = 24)</td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>71</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>CR</td>
<td>57</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>Month 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>43</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>CR</td>
<td>43</td>
<td>50</td>
<td>36</td>
</tr>
</tbody>
</table>

- Most response to KTE-C19 observed by first assessment
- 7 pts with SD/PD at 1 mo converted to CR at month 3
- 1 PR converted to CR at month 9
- 4 patients did not have a month 6 assessment prior to data cut off
- Median follow –up: 8.7 months

Median age 59
No. of prior therapies: 3 (1-12)
Met primary endpoint of ORR at 3 and 6 month interim analysis (vs assumed historical control of 20%; exact binomial test: $P < .0001$)

ZUMA-1: Safety (Phase 2)

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>DLBCL (n = 73)</th>
<th>PMBCL/TFL (n = 20)</th>
<th>All Pts (N = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 AE</td>
<td>68 (93)</td>
<td>18 (90)</td>
<td>86 (92)</td>
</tr>
<tr>
<td>Grade ≥ 3 CRS</td>
<td>10 (14)</td>
<td>2 (10)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Grade ≥ 3 NE</td>
<td>18 (25)</td>
<td>9 (45)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Fatal events (no PD)*</td>
<td>1 (1)</td>
<td>2 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>1 (1)</td>
<td>2 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>• KTE-C19 related†</td>
<td>1 (1)</td>
<td>2 (10)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>• KTE-C19 unrelated‡</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

- CRS and NEs typically reversible
  - CRS: all events resolved except 1 cardiac arrest case in cohort 2
  - NEs: 3 ongoing at cutoff (grade 1: memory impairment, tremor; grade 2: tremor), 1 death from PD with ongoing NE
  - Pts treated with tocilizumab (38%), corticosteroids (17%), or both (17%)

- No cerebral edema events

*2 fatal events related to KTE-C19.
†1 HLH (cohort 1), 1 cardiac arrest (cohort 2) in the setting of CRS.
‡Pulmonary embolism (cohort 2).

Slide credit: clinicaloptions.com
CAR T in MM

- **Targets:** CD19, BCMA, CS1, NKG2D

<table>
<thead>
<tr>
<th>Study</th>
<th>CAR/costim</th>
<th>Dose</th>
<th>Response</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPENN N=6</td>
<td>BCMA 4-1BB</td>
<td>100 to 500M 10- 50M+Cy 100-500M+Cy</td>
<td>1 CR, 1 VGPR of 6</td>
<td>CRS in 5: 2 gr3 1 gr 4 PRES</td>
</tr>
<tr>
<td>NCI N=12</td>
<td>BCMA 4-BB</td>
<td>0.3 to 9x10^6/kg</td>
<td>DL1-3(N=9): 1 VGPR DL4 (N=3):1 CR, 1 VGPR</td>
<td>1 Gr. 3 CRS &amp; delirium in DL4</td>
</tr>
<tr>
<td>CRB-401 BluebirdBio N=11</td>
<td>BCMA 4-BB</td>
<td>50M 150M 450M 800M</td>
<td>DL1:1 SD, 1 PR, 1 PD DL2:1 CR, 1 VGPR, 2 MRD- CR DL3: 3 PR</td>
<td>No DLT No ≥gr3 CRS or NE</td>
</tr>
</tbody>
</table>
Resistance to CD19CAR T Treatment

- No response
  no T cell proliferation (T cell intrinsic mechanism)

- CD19- relapse: 20 to 67% of recurrence
  7/18 (39%) CD19-ve relapse in SCH B-ALL studies

- Short CAR T persistence
  immunogenicity?

Grupp, ASH 2015
Turtle, ASH 2015
Gardner ASH 2016
CD19CAR Trial for aggressive B-NHL in aSCT setting

- COH:CD19-28 CAR NHL3
  PI: Leslie Popplewell, MD
  Pts: transplant eligible
  CAR T: Tcm or Tcm+Tn
given on day 2
dose escalation: 50M, 200M, 600M

Results
Formal analysis not performed yet
No death
CRS and neurotoxicity observed

- MSKCC:JCAR 015
  PI: Craig Saulter, MD
  Pts: detectable disease prior to aSCT
  CAR T: pbmc-derived
given on day 2 and day 3
Dose escalation: 5M/kg, 10M/kg, 20M/kg

Results
Interim results presented at ASCO 2015
7/11 grade 3 &4 CRS (MS changes)
1 pt died from infection
Efficacy Summary

- CD19CAR T cell mediates potent anti-tumor effect
- Response does not correlate with CD19 expression density, disease risk factors, or disease burden.
- High CNS penetration. Advanced CNS disease can be treated without severe neurotoxicity.
- Post treatment relapse are linked to early loss of CAR T cells generation of CD19- variants.
CAR T Cell Therapy: Complications

Commonly reported important adverse events

- On target off tumor effects, i.e. B cell aplasia
- Lymphodepletion chemo related toxicity
- Tumor lysis syndrome
- Macrophage activation syndrome (HLH/MAS)
- Cytokine release syndrome
- Neurotoxicity
B Cell Aplasia

- On target, off tumor effect
  CD19 expresses throughout normal B cell development

- Clinical outcome
  - indicator for CD19CAR T cell persistence and response
  - hypogammaglobulinemia (serum IgG < 400 or 500 mg/dl)
    - No significant increase of severe infection

- Management
  - ivig replacement if IgG less than 400 mg/dl
Cytokine Release Syndrome

• A constellation of inflammatory symptoms from cytokine elevations.
• Association with T cell activation and proliferation in T cell-engaging therapies.
• Association with clinical benefit.
• CRS-related death reported after Blinatumomab and CAR T treatment.
## Clinical Signs and Symptoms Associated with CRS

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinogenemia ± bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures</td>
</tr>
</tbody>
</table>

Lee DW et al. Blood 2014
Correlates of severe cytokine release syndrome (CRS)

Correlates with Severe CRS

- Pre-T cell infusion tumor burden
- CAR T expansion post infusion

Maude et al. NEJM 2014
CRP is a Good Biomarker for CRS

Fig. 4. CRP levels in patients infused with 19-28z CAR T cells.

## CRS Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever ± symptoms such as rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache</td>
</tr>
<tr>
<td></td>
<td>Hypotension responding to fluid resuscitation or one low dose pressor, or</td>
</tr>
<tr>
<td>2</td>
<td>Hypoxia responding to ≤ 40% FiO2, or Grade 3 transaminitis, other grade 2 organ toxicity according to CTCAE v4.03</td>
</tr>
<tr>
<td>3</td>
<td>Hypotension requiring &gt;3 hours of two pressors, or one pressor at high dose, or</td>
</tr>
<tr>
<td></td>
<td>Hypoxia requiring &gt;40% FiO2, or Grade 4 transaminitis, other grade 3 organ toxicity according to CTCAE v4.03</td>
</tr>
<tr>
<td>4</td>
<td>Requirement of mechanical ventilator support, or Grade 4 organ toxicity excluding grade 4 transaminitis</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Lee DW et al. Blood 2014
COH CRS treatment algorithm

Grade 1 CRS

- Monitor for CRS symptoms including vital signs & neurologic changes at least q 8 hours
- Follow serum CRP, CMP, UA, LDH, PT/INR/PTT
- Conduct infectious disease work-up
- Empiric antibiotics coverage as appropriate
- Medical supportive measures as appropriate

Grade 2 CRS

- CRP > 200mg/l
- Monitor for CRS symptoms including vital signs & neurologic changes at least q 4 hours
- Follow serum CRP, CMP, UA, LDH, Ferritin, PT/INR/PTT
- Conduct infectious disease work-up
- Medical supportive measures as appropriate
- Tocilizumab 4-8mg/kg IV indicated in patients with persistent fever, grade 2 neurotoxicity, or hypotension greater than 7 days or patients older than 60.

Grade 3 CRS

- ICU monitor
- Follow serum CRP, CMP, UA, LDH, Ferritin, PT/INR/PTT
- Vigilant medical supportive measures
- Tocilizumab 4-8mg/kg IV
- If no improvement within 12 hours, start dexamethasone 10mg IV Q 12 hours until improvement
- If predominant neurotoxicity, start dexamethasone instead of tocilizumab

Grade 4 CRS

- ICU monitor
- Vigilant medical supportive measures
- Follow serum CRP, CMP, UA, LDH, Ferritin, INR/PTT
- Tocilizumab 4-8mg/kg IV. May repeat in 12 to 24 hours
- AND Dexamethasone 10mg IV Q 12 hours or methylprednisolone 1mg/kg Q12 hours until improvement
CRS Management

**Goal:** reduce serious CRS symptoms and signs and **prevent life-threatening complications**

- Tocilizumab is the first choice for severe CRS (selective grade 2, all grade 3 and 4 cases).
  
  humanized IgG1 anti-hIL-6R mAb
  
  4 - 8 mg/kg iv over 1 hour x1, can repeat in 24 to 48 hours
  
  AE: <1% grade 3 AST/ALT elevation; <1% grade 3 cytopenia

*Would prophylactic tocilizumab increase safety without compromising efficacy?*

*What to do in tocilizumab refractory cases (no improvement after 2 doses of Tocilizumab)?*

Steroids, Methylpred 2mg/kg/d or Dex 0.5mg/kg max 10mg/dose, quick taper.

siltuximab
Neurologic Toxicity

AEs: encephalopathy, delirium, aphasia, ataxia, confusion, hallucinations, headaches, tremor, seizure, obtundation
Can occur independently from CRS or presence of CAR T cells in CSF
Can lead to patient death (ROCKET JCAR015 trial)

Management:
- CSF, CT or MRI study.
- Supportive care (fluid, electrolytes, avoid drugs with CNS toxicity).
- Dex is the drug of choice. Consider slow taper.
Patient Eligibility Considerations

• Adequate lymphocyte numbers
  - some trials use a cut off of 100 - 500 ALC/ul
• Relative disease stability
  - Product ready time 2 - 4 weeks
• No h/o autoimmune disease, CVA, seizure, CNS involvement (not absolute contraindication)
• Good performance and organ function
  - physically able to deal with CAR T toxicities
• Willingness to take risks
  - life threatening complications
  - prolonged neurologic changes
Patient Eligibility Considerations

- Prior treatment
  Prior Blinatumomab?
  - no impact on efficacy as long blasts remain CD19+
  Prior Allogeneic HCT?
  - no impact on CAR efficacy
  Prior CD19 CAR T
  - might still respond to a different CAR T treatment
    - CTL119, CD22 CAR
  - prolonged neurologic changes
Novel CAR T Manufacture And Process
Approaches to Improve CAR T-cell Therapy

- More potent
- More controllable
- Shorter Production time

Questions?

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