Taking Aim with CAR T: Commercial CAR T-cell Therapy in Diffuse Large B-Cell Lymphoma

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October 13th, 2018

Disclosures
• No conflicts of interest

Objectives
• Describe the mechanism of action of commercial CAR T-cell therapies, axicabtagene ciloleucel (Axicel) and tisagenlecleucel
• Review the clinical efficacy, safety, and place in therapy of CAR T-cell therapy in diffuse large b-cell lymphoma (DLBCL)
• Discuss the monitoring and the management of potential adverse effects of CAR T-cell therapy
• Review the logistical factors that play a role in treating patients with commercial CAR T-cell therapies

Types of Immunotherapy
• Vaccination
  • Sipuleucel-T, Calmette-Guerin (BCG), talimogene laherparepvec (T-VEC)
• Cytokine Therapy
  • Interleukin, Interferons
• Monoclonal Antibodies
  • Bispecific T-cell engagers (BiTE)
  • Check point inhibitors: PD-1, PDL-1, CTLA-4 inhibitors
• Adoptive Cellular Therapy
  • Chimeric antigen receptor T-cell therapy

Concepts of Immunotherapy in Cancer
• The human’s immune system is capable of noticing differences in protein structure and recognizing foreign and neoplastic cells
• Tumors develop multiple resistance mechanisms to escape immune recognition and subsequent target destruction
  • Local immune evasion
  • Induction of tolerance
  • Systemic disruption of T-cell signaling
• Immunotherapy utilizes the body’s own immune system in various mechanisms to repair, stimulate, or enhance the body’s natural immune response

Adoptive Cellular Therapy
• First studied in melanoma patients in 1980’s
• Main barriers included:
  • Difficulty in culturing & manufacturing of tumor-infiltrating lymphocytes
  • Immune tolerance to self-antigens
  • Requirement for major histocompatibility complex (MHC) presentation of antigens
CAR T-cell Therapy

- Genetically modified T-cells to express chimeric antigen receptors (CARs)
- Bind to specific tumor cell surface antigens
- Act independently of MHC

Advantages of CAR T-cell Therapy

- Circumvent immune tolerance of T-cell & MHC restriction
- Limited off-target effects
- Specific to certain types of cancers
- Rapid onset of action
- Potential long-term disease control

CAR T-cell Therapy Overview

- First Generation CAR
  - Extracellular binding domain
    - Single-chain variable fragment (scFv)
  - Transmembrane domain
    - CD8α or CD28
  - Intracellular signaling domain
    - CD3ζ (CD3Zeta)

- Second Generation CAR:
  - Contain one co-stimulatory domain (CD28 or 4-1BB [CD137])
  - Improve proliferation & cytokine secretion
  - Resistance to apoptosis
  - In vivo persistence

- Third Generation CAR:
  - Contain two co-stimulation domains
    - CD28
    - 4-1BB (CD137)
    - CD27
    - ICOS
    - OX40 (CD134)

CAR T-cell Therapy Targets

- CD19 ubiquitously expressed on B-cells
- CD20 expression maintained in most B-cell malignancies
- Other hematologic/malignancy targets
- B-cell maturation antigen (BCMA), CD22, CD30, CD133, CD338

Lymphodepletion (Conditioning Regimen)

- Administered prior to CAR T-cell infusion

Rationale

- Decrease disease burden
- Enhance CAR T-cell in-vivo expansion and function
- Increase CAR T-cell persistence
- Depletion of regulatory T cells that may interfere with adoptive T cell activity → greater engraftment of infused T-cells

Lymphodepleting Regimen

- Cyclophosphamide + Fludarabine x 3 days
- Bendamustine
FDA Approved CAR T-cell Therapy in DLBCL

FDA Approved CAR T-cell Therapy Products

<table>
<thead>
<tr>
<th>FDA Approved CAR T-cell Therapy Products</th>
<th>Axi-cel (KTE-C19)</th>
<th>Tisagenlecleucel (CTO19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphodepletion Regimen</strong></td>
<td>Required: Flu/Cy</td>
<td>If needed: Flu/Cy or Bendamustine</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>2 x 10^6 CAR T-cells/kg (Max. 2 x 10^7 CAR T-cells)</td>
<td>DLBCL: 0.6 to 6 x 10^6 CAR T-cells</td>
</tr>
<tr>
<td><strong>REMS</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>BBW</strong></td>
<td>Cytokine Release Syndrome (CRS) &amp; Neurologic Toxicity</td>
<td>Cytokine Release Syndrome (CRS) &amp; Neurologic Toxicity</td>
</tr>
<tr>
<td><strong>Pre-Medications</strong></td>
<td>APAP &amp; H1-antihistamine</td>
<td>APAP &amp; H1-antihistamine</td>
</tr>
</tbody>
</table>

### ZUMA-1 Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=101)</th>
<th>DLBCL (N=77)</th>
<th>PMBCL or TFL (N=24)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), yr</td>
<td>58 (23-79)</td>
<td>58 (23-79)</td>
<td>57 (25-75)</td>
</tr>
<tr>
<td>Male –no. (%)</td>
<td>68 (67)</td>
<td>50 (65)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>ECOG PS 1 – no. (%)</td>
<td>59 (58)</td>
<td>49 (64)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Disease Stage III or IV – no. (%)</td>
<td>86 (85)</td>
<td>67 (87)</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Prior therapies – no. (%)</td>
<td>70 (69)</td>
<td>49 (64)</td>
<td>21 (88)</td>
</tr>
<tr>
<td>Primary refractory disease</td>
<td>26 (26)</td>
<td>23 (30)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Resistance to 2 consecutive lines</td>
<td>54 (53)</td>
<td>39 (52)</td>
<td>15 (62)</td>
</tr>
</tbody>
</table>

*PMBCL: Primary Mediastinal B-cell lymphoma; TFL: Follicular Lymphoma

### ZUMA-1 Trial: Efficacy Results

At 15.4 months

**Endpoint Definition**

Primary: Objective Response Rate (CR + PR)
Secondary: OS, duration of response, PFS, safety, biomarker assessments

**Population**

- ≥ 18 years
- ≥2/ Large B-cell lymphoma (DLBCL, PMBCL, TFL)
  - ECOG PS 0-1
  - Adequate renal, hepatic, pulmonary & cardiac function (N=111)

**Treatment**

- Lyphodepletion: Flu/Cy
- Axi-cel
  - < 100kg: target dose 2 x 10^6 CAR T-cells/kg
  - ≥ 100kg: fixed dose 2 x 10^6 CAR T-cells/kg (N=101)
ZUMA-1 Trial: Efficacy Results

- Median duration of response: 11.1 months
- Median PFS: 5.8 months
- Median OS: Not reached

JULIET Trial: Single-arm, open-label, multicenter, global phase II trial

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 18 years</td>
<td>Bridging therapy/lymphodepletion*</td>
</tr>
<tr>
<td>Received ≥ 2 lines of chemotherapy</td>
<td>Tisagenlecleucel (median 3.1 x 10⁸ cells)</td>
</tr>
<tr>
<td>Ineligible for or failed ASCT (N=165)</td>
<td>(N=111)</td>
</tr>
</tbody>
</table>

JULIET Trial: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>56 (22-76)</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>76%</td>
</tr>
<tr>
<td>Double/Triple hits in MYC/BLC2/BCL6</td>
<td>17%</td>
</tr>
<tr>
<td>Germinal Center B-cell</td>
<td>57%</td>
</tr>
<tr>
<td>Activated B-cell</td>
<td>41%</td>
</tr>
</tbody>
</table>

JULIET Trial: Efficacy Results

- ORR (at 14 months): 52%
  - CR: 40%
  - PR: 12%
- Median Duration of Response (at 14 months): not reached
- Probability of relapse free
  - At 6 months: 74%
  - At 12 months: 65%
- Median OS: 11.7 months

Place in Therapy

- CAR-T Therapy: “Fit”
  - ECOG Grade 0-1
  - No major comorbidities
  - No CNS involvement
  - Adequate renal/hepatic function

CAR T-cell Therapy Adverse Effects
Cytokine-Associated Toxicities of CAR T-cell Therapy – Black Box Warnings

Cytokine Release Syndrome (CRS)

Neurotoxicity

Cytokine Release Syndrome (CRS)

• Most common acute and potentially serious toxicity of CAR T-cell therapy
• Non-antigen-specific inflammatory response that occurs as a result of high-level immune activation

- Elevated cytokines
  - Interleukin-6 (IL-6)
  - Interferon-γ, Tumor necrosis factor
  - IL-2, IL-2 receptor-α, IL-8, IL-10
- Elevated inflammatory markers
  - Ferritin
  - C-reactive protein (CRP)

CRS Overview

• Most common acute and potentially serious toxicity of CAR T-cell therapy
• Non-antigen-specific inflammatory response that occurs as a result of high-level immune activation

- Elevated cytokines
  - Interleukin-6 (IL-6)
  - Interferon-γ, Tumor necrosis factor
  - IL-2, IL-2 receptor-α, IL-8, IL-10
- Elevated inflammatory markers
  - Ferritin
  - C-reactive protein (CRP)

Signs & Symptoms Associated with CRS

- Fever = Hallmark Symptom!
  - Usually 1st symptom of CRS
- Monitoring
  - Temperature
  - BP, HR
  - O2 saturation
  - End organ failure
  - CRP, Ferritin

Organ System Symptoms

Constitutional
- Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache

Cardiovascular
- Tachycardia, hypotension, arrhythmias, QT prolongation, decreased LVEF, widened pulse pressure, tachypnea

- Other symptoms: pulmonary (respiratory distress syndrome, hypoxia), renal and/or hepatic failure, DIC, neurologic toxicity

Incidence of CRS

• Incidence, time of onset and severity varies between disease states, products & dose
• Typically occurs within first 1-2 weeks after CAR T-cell infusion

<table>
<thead>
<tr>
<th>Trial</th>
<th>Product</th>
<th>Grade</th>
<th>Time of onset</th>
<th>Median time until resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>Axicel</td>
<td>Any: 93% Grade ≥ 3: 13%</td>
<td>Median: 2 days</td>
<td>Range: 1-12 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median: 8 days</td>
<td>Range: 2-58 days</td>
</tr>
<tr>
<td>JULIET*</td>
<td>Tisagenlecleucel</td>
<td>Any: 58% Grade ≥ 3: 12%</td>
<td>Median: 3 days</td>
<td>Range: 1-8 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median: 7 days</td>
<td>Range: 3-34 days</td>
</tr>
</tbody>
</table>


Risk Factors for Severe CRS

- High disease burden
- Early onset CRS (≤ 3 days)
- Multiple co-morbidities
- Older age
- Elevated baseline CRP
- Higher Cell Dose
- Increased CRP & Ferritin

Patient Case Continued

- PJ is a 53 y.o relapsed DLBCL s/p R-CHOP, RICE, auto HSCT
  - Required 2 courses of steroids for high disease burden and enlarging lymph nodes prior to CAR T-cell infusion
- PJ is Day +3 from receiving Axicel infusion

<table>
<thead>
<tr>
<th>Vitals/Labs</th>
<th>Day -1</th>
<th>Day 0</th>
<th>Day +1</th>
<th>Day +2</th>
<th>Day +3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>98</td>
<td>101</td>
<td>128</td>
<td>124</td>
<td>118</td>
</tr>
<tr>
<td>BP</td>
<td>114/73</td>
<td>96/65</td>
<td>110/76</td>
<td>120/82</td>
<td>115/72</td>
</tr>
<tr>
<td>O2 Sat</td>
<td>98%</td>
<td>97%</td>
<td>100%</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>Fever (°F)</td>
<td>98.4</td>
<td>99</td>
<td>100.8</td>
<td>102.5</td>
<td>101.3</td>
</tr>
<tr>
<td>CRP (0-3mg/L)</td>
<td>77</td>
<td>57</td>
<td>38</td>
<td>82</td>
<td>59</td>
</tr>
</tbody>
</table>
Grading of CRS

**Grading of CRS - 2014 Lee DW et al.**

**Key Factors in CRS Grading**

<table>
<thead>
<tr>
<th>Constitutional Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
</tr>
<tr>
<td>O2 Requirements</td>
</tr>
<tr>
<td>Sx of end organ failure</td>
</tr>
</tbody>
</table>

**Comparison of CRS Grading Scales**

<table>
<thead>
<tr>
<th>Grade</th>
<th>2014 Lee DW et al.</th>
<th>Penn Grading Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Sx. require symptomatic sx only</td>
<td>Mild reaction; tx w/ supportive care</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hypotension requiring high O2 or O2 requirement &gt; 40% FiO2</td>
<td>Moderate reaction; some signs of organ dysfunction related to CRS &amp; not attributable to any other condition</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe reaction &amp; require to organ dysfunction</td>
<td>Hospitalization for management of CRS-related symptoms</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening sx or</td>
<td>More severe reaction; Hospitalization</td>
</tr>
</tbody>
</table>

**Management of CRS**

**Supportive Care (all grades)**
- Anti-pyretics, pain control, O2 supplementation, IV fluids, vasopressors

**Tocilizumab (Grade 2+)**
- Anti-IL-6 receptor (inhibits IL-6 signaling)
- FDA approved in Aug 2017: CARD T cell induced severe or life threatening CRS
- 8 mg/kg (max 800mg) IV over 1 hour x1 dose, then q8h PRN CRS (for children <30kg, 12 mg/kg (max 800mg)
- Limit 3 doses w/in 24 hours for max of 4 total doses
- Caution in hepatic impairment

**Corticosteroids (Grade 3+ or unresponsive Grade 2)**
- Suppresses inflammatory response and reduces T cell apoptosis
- Methylprednisolone or (dexamethasone) – dose depends on severity
- Continue until c Grade 2, then taper over 3 days

**Management of CRS – Lee DW et al.**

**Concomitant supportive care!**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Grade 2</td>
<td>✓</td>
<td>(if no improvement w/in 24 hours after tocilizumab, start steroids per grade 3)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>✓</td>
<td>Methyprednisolone 1 mg/kg x twice daily (or dexamethasone equivalent)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>✓</td>
<td>Methyprednisolone 1000 mg IV daily x 3 days (or dexamethasone equivalent)</td>
</tr>
</tbody>
</table>

**Institutional specific guidelines**

- Sx, require symptomatic sx only (eg, fever, nausea, fatigue, headache, myalgia, malaise)
- Sx, require & respond to moderate intervention and
  - O2 requirement < 40% FiO2
  - Hypotension responsive to fluids or low-dose of one vasopressor
  - Grade 2 organ toxicity
- Sx, require & respond to aggressive intervention and
  - O2 requirement >40% FiO2
  - Hypotension requiring high-dose or multiple vasopressors
  - Grade 3 organ toxicity
  - Grade 4 transaminitis
- Life-threatening sx and
  - Require ventilator support, CVVHD or
  - Grade 4 organ toxicity (excluding transaminitis)

**Management of CRS**

- Anti-pyretics, pain control, O2 supplementation, IV fluids, vasopressors
Incidence of Tocilizumab & Management

<table>
<thead>
<tr>
<th>Trial</th>
<th>Product</th>
<th>Tocilizumab</th>
<th>Glucocorticoids</th>
<th>Vasopressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>Axi-cel</td>
<td>43%</td>
<td>27%</td>
<td>17%</td>
</tr>
<tr>
<td>JULIET</td>
<td>Tisagenlecleucel</td>
<td>15%</td>
<td>11%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Some data taken from earlier interim analysis

Anti-IL-6 Therapy: Siltuximab

- **MOA**
  - Recombinant humanized anti-human IL-6 receptor monoclonal antibody that binds to IL-6

- **FDA indication**
  - Castleman disease

- **Dose**
  - 11mg/kg IV x 1 dose
  - No dose adjustments

*Used off label for CRS refractory to Tocilizumab

Incidence of Neurotoxicity

<table>
<thead>
<tr>
<th>Trial</th>
<th>Product</th>
<th>Grade</th>
<th>Time of onset</th>
<th>Median time until resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA-1</td>
<td>Axi-cel</td>
<td>Any: 64% Grade ≥ 3: 28%</td>
<td>5 days</td>
<td>5-17 days</td>
</tr>
<tr>
<td>JULIET</td>
<td>Tisagenlecleucel</td>
<td>Any: 21% Grade ≥ 3: 12%</td>
<td>6 days</td>
<td>1-359 days</td>
</tr>
</tbody>
</table>

Patient Case Continued

- PJ is Day +18 from receiving Axi-cel infusion.
  - His symptoms of CRS have completely resolved.
  - However, during rounds, PJ is complaining of headaches and confusion overnight. He is only able to identify the year and city, but not the hospital, month & current president’s name.
  - PJ is also having difficulty identifying objects near him.
  - The team is concerned that PJ is experiencing neurotoxicity 2° to his CAR T-cell infusion.

CAR T-cell Induced Neurotoxicity

- **May occur with or without CRS**
  - Severe neurologic events may be more frequent with higher grade CRS

- **Signs & symptoms**
  - Headache, confusion, alteration in wakefulness, hallucinations, delirium, tremor, agitation, somnolence
  - Focal neurologic deficits, generalized encephalopathy, dysphasia, ataxia, apraxia, facial nerve palsy, seizures

- **Pathophysiology**
  - Exact mechanism not completely elucidated
  - CAR T-cells may cross the blood-brain barrier
  - Early onset of high serum cytokines (IL-6, IFN-γ, TNF-α)

Management of Neurotoxicity

- **Grade 2**
  - Somnolence (moderate), confusion (moderate), encephalopathy, dysphasia, seizures
  - Dexamethasone 10mg IV Q6H
  - Tocilizumab for G2 CRS
  - If no improvement within 24 hrs. → dexamethasone 10mg IV Q6H

- **Grade 3**
  - Somnolence (obtundation, stupor), confusion (severe), encephalopathy, dysphasia
  - Same as Grade 2
  - Tocilizumab for G2 CRS
  - Dexamethasone: 10mg IV Q6H with 1st dose of tocilizumab

- **Grade 4**
  - Life-threatening consequences, urgent intervention, requirement for mechanical vent, consider central sedation
  - Methylprednisolone 1000mg IV/day for 3 days
  - Tocilizumab for G2 CRS
  - Methylprednisolone 1000mg IV/day for 1st dose of tocilizumab & continue x 2 days
  - If improvement, then manage as above

  - Consider non-sedating, anti-seizure medications for seizure prophylaxis
  - Continue dexamethasone use until the event ≤ Grade 1, then taper over 3 days

*per Axi-cel PI
CRS and Neurotoxicity Monitoring

<table>
<thead>
<tr>
<th>CRS</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitals</td>
<td>Daily neuro exams</td>
</tr>
<tr>
<td>Temperature</td>
<td>Hospitalization for 27 days required following infusion</td>
</tr>
<tr>
<td>BP, HR</td>
<td>Patients must remain within close proximity to the treating hospital/clinic for 24 weeks</td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>Driving restrictions</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>LFTs</td>
<td></td>
</tr>
<tr>
<td>Scr</td>
<td></td>
</tr>
<tr>
<td>Inflammatory Markers</td>
<td></td>
</tr>
<tr>
<td>CRP, Ferritin</td>
<td></td>
</tr>
</tbody>
</table>

Other Acute Toxicities of CAR T-cell Therapy

- Hypersensitivity
  - Pre-medicate prior to infusion
- Tumor Lysis Syndrome
  - Allopurinol for TLS prophylaxis
  - Monitor electrolytes + uric acid
- Fever/Serious Infections/Febrile Neutropenia
  - Consider prophylactic anti-microbials & GCSF per institutional guidelines
  - Empiric ID workup
- GI Toxicity (N/V/D)
  - Anti-emetic agents PRN
  - Anti-diarrheal agents PRN (r/o infectious causes)
- Hematologic
  - Transfusion support
- Fatigue/Decreased Appetite
- Headache

Long-Term Toxicities of CAR T-cell Therapy

- Prolonged cytopenias
  - May persist for several weeks following lymphodepletion & CAR T-cell infusion
- B-Cell Aplasia
  - Hypogammaglobulinemia
- Secondary Malignancies
  - Monitor life-long
- Viral Reactivation

Logistical Factors with Commercial CAR T-cell Therapies

Logistical Factors

- REMS Requirements
- Timing and Logistics
- Financial Implications

REMS Requirements

- Goals of the REMS Program are to mitigate the risks of CRS and neurologic toxicities by...
  1. Ensuring that hospitals & their associated clinics that dispense CAR T-cell therapy are specially certified & have on-site, immediate access to a minimum of 2 doses of tocilizumab for each patient within 2 hours after CAR T-cell infusion
  2. Ensuring that those who prescribe, dispense, or administer CAR T-cell therapy are aware of how to manage the risks of CRS & neurologic toxicities
REMS Pharmacy Considerations

- Anticipating adequate supply of tocilizumab
- Length of stay
- Number of potential patients initiating therapy
- Space
- Documentation and Workflow
  - Institutional standard operating procedure (SOP) for documentation
  - Staff education/training
- Cost

REMS Program Patient Wallet Card

- Given to all patients prior to dispensing CAR T-cell therapy
- Patients/guardians must carry with them at all times

- Purpose:
  - To remind patients of sx of CRS & neurological toxicities that require immediate medical attention
  - To remind patients to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following infusion

Timing & Logistics

Task 1. Patient Referral, Selection, Evaluation
- Insurance approval
- J/O DLBCL symptom control: Need bridging treatment strategies?

Task 2. CAR-T cell Collection
- FDA-registered apheresis & cell-processing facilities

Task 3. CAR-T cell Production
- Ship apheresis product to manufacturer
- Time to manufacture product: ~1 month

Task 4. CAR-T cell Infusion & post-infusion care
- Lymphodepletion regimen
- Planned hospital admission

Lymphodepletion Regimens

<table>
<thead>
<tr>
<th>Product</th>
<th>Regimen</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi-cel</td>
<td>Cyclophosphamide 500mg/m² IV daily x 3</td>
<td>-5, -4, -3</td>
</tr>
<tr>
<td></td>
<td>Fludarabine 30mg/m² IV daily x 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± Mesna &amp; GCSF support ¹</td>
<td></td>
</tr>
<tr>
<td>Tisagenleu胞el</td>
<td>Cyclophosphamide 250mg/m² IV daily x 3 days</td>
<td>CAR T-cell infusion must be ≥ 11 days post completion of chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Fludarabine 25mg/m² IV daily x 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± Mesna &amp; GCSF support ²</td>
<td></td>
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<tr>
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<td>Alternative regimen*</td>
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<td>Bendamustine 90mg/m² IV daily x 2 days</td>
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</tbody>
</table>

Lymphodepletion may be omitted if WBC ≤ 1 x 10⁹ within 1 week prior to CAR T-cell infusion
*May use alternative regimen: if experienced previous Grade 4 hemorrhagic cystitis w/ cyclophosphamide or demonstrative resistance to a previous cyclophosphamide-containing regimen
*Induction specific

Timeline of Axi-Cel

- Days -5 to -3: Lymphodepletion (DFCI)
- Day -1: Admitted to BWH
- Day 0: Axi-cel infusion
- Day ≥ 8+: Discharge

Multidisciplinary Care

- Hematology & Oncology
- Neurology
- Nephrology
- Nursing
- Pharmacy
- Mid-Level Providers
- Patient Care Coordination
- Interventional & Critical Care
- Cardiology
- Finance
Patient Case Continued

- PJ is a 53 y.o relapsed DLBCL s/p R-CHOP, RICE, auto HSCT
- Required 2 courses of steroids for high disease burden and enlarging lymph nodes prior to CAR T-cell infusion
- PJ is Day +3 from receiving Axi-cel infusion

Patient Case Continued

- PJ is Day +18 from receiving Axi-cel infusion.
- His symptoms of CRS have completely resolved.
- However, during rounds, PJ is complaining of headaches and confusion overnight. He is only able to identify the year and city, but not the hospital, month & current president’s name. PJ is also having difficulty identifying objects near him.
- The team is concerned that PJ is experiencing neurotoxicity 2° to his CAR T-cell infusion.

Vitals/Labs | Day -1 | Day 0 | Day +1 | Day +2 | Day +3
---|---|---|---|---|---
HR | 98 | 101 | 128 | 124 | 118
BP | 114/73 | 96/65 | 110/76 | 120/82 | 115/72
O2 Sat | 98% | 97% | 100% | 97% | 98%
Fever (°F) | 98.4 | 99 | 100.8 | 102.5 | 101.3
CRP [0-3mg/L] | 77 | 57 | 38 | 62 | 59

Conclusion

- Two anti-CD19 directed CAR T-cell therapies are now FDA approved for patients with relapsed/refractory DLBCL
- Continued education for monitoring and early management of CAR T-cell therapy adverse events are needed
- Optimal care of patients receiving CAR T-cell therapy requires a multidisciplinary approach
- Further research is being conducted to find the optimal CAR design to minimize adverse events related to immune-activation and maximize long-term efficacy

Taking Aim with CAR T: Commercial CAR T-cell Therapy in Diffuse Large B-Cell Lymphoma

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October 13th, 2018