Patient Considerations for CAR T Cell Therapy

Module 2
Patient Identification

1. Appropriate patients will be identified for treatment at qualified treatment sites or referring sites.
2. Company will be notified and leukapheresis and treatment dates will subsequently be scheduled.

Leukapheresis

3. The CAR T cell product is created at a manufacturing facility.
4. Patients may require bridging therapy to maintain disease control while the CAR T cell product is being manufactured.
5. The CAR T cell product is delivered to the treatment site.
6. The patient is monitored closely for at least 4 weeks and side effects are promptly managed. Caregiver support is critical during this time.

Post hospital discharge monitoring

Long-term monitoring

Patient Considerations for CAR T Therapy

- 01 Patient Evaluation
- 02 Select Considerations Around CAR T Cell Infusion
- 03 Patient Characteristics and Outcomes
- 04 Bridging Therapy and Prior Treatment Effects on Patient Outcomes
Coordination Between Primary Hematologist and CAR T Cell Treatment Team

**Primary Hematologist**
- Refers the patient for CAR T cell therapy

**CAR T Cell Treatment Team**
- The clinical staff at a qualified treatment facility

- Patient assessment begins with the primary hematologist:
  - It is important that primary physicians be knowledgeable of the eligibility criteria for CAR T cell therapy.
  - Medical records, including pathology reports, historical imaging, laboratory values, treatment history, and other salient information should be provided by the referring provider for consideration by the CAR T cell treatment team.

- Referred patients meet with members of the CAR T treatment team to determine if CAR T cell therapy is right for them.
- Efficient pre-screening of patients can expedite the next step in therapy for the patient, whether that be undergoing apheresis for CAR T cell therapy or receiving another therapeutic option.

After referral to a CAR T cell treatment center, patient workup may include:

- Review of medical and treatment history\(^1,2\)
  - May require confirmatory biopsy of disease if not recently completed or reviewed\(^2\)
- Assessment of organ function, comorbidities, and performance status\(^1\)
- Laboratory studies\(^2\)
  - CRP, ferritin, LDH, CBC with differential, comprehensive metabolic panel\(^2\)
  - Screening for infections including hepatitis B, hepatitis C, and HIV\(^3\)

References:
Considerations for CAR T Cell Therapy

General considerations for candidates for CAR T cell therapy:

- Have a disease as defined in commercial indication or in clinical trial\(^1\)
- Adequate marrow function\(^2\)
- Adequate patient fitness, performance status, and organ function\(^3\)
- No active, uncontrolled infections, including hepatitis B, hepatitis C, or HIV\(^3\)
- Absence of clinically relevant comorbidities (eg, select cardiovascular, neurologic, or immune disorders)\(^3\)
- Cumulative chemotherapy exposure may adversely affect quality of circulating T cells\(^2\)
  - Eg, bendamustine may adversely affect T cell numbers and function\(^4\)
- Allogeneic stem cell transplant before CAR T cell therapy increases the risk of GVHD because the manufactured CAR T cells will be derived mostly from the engrafted donor T cells\(^5\)

Additional considerations:

- Socioeconomic factors\(^1\)
- Caregiver support - a dedicated caregiver should be available 24 hours a day\(^6\)
- Social work evaluation\(^7\)
- Stay in close proximity of treating institution for at least 4 weeks after CAR T cell infusion\(^6\)

GVHD, graft-versus-host disease.

References:
Considerations For CAR T Cell Therapy May Differ From Criteria For Stem Cell Transplants

It is important to recognize that eligibility for CAR T cell therapy may differ from criteria for stem cell transplants.

General considerations for candidates for stem cell transplant:
- Age
- Adequate patient fitness, performance status, and organ function
- Tolerant of high doses of chemotherapy
- Chemosensitivity (precise recommendations may vary by institution)

Additional considerations:
- Socioeconomic factors
- Caregiver support
- Social work evaluation

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Washout Periods Prior to Apheresis

The washout period prior to apheresis is critical to ensure a sufficient number of cells can be collected for CAR T cell manufacturing.1

• Pre-apheresis washout periods may vary based on agent:
  – Chemotherapy (typically 2 weeks)2
  – Immunomodulatory drugs (typically 2 weeks)2
  – Immunosuppressants (typically earliest possible stop time)2
  – Steroids (typically greater than 72 hours)2
  – Radiation is lymphodepleting and should be delivered after apheresis. Radiation therapy is not recommended prior to apheresis.3,4
  – Alkylating agents may require washout periods up to 6-9 months due to potential detrimental effects on apherased PBMCs.5
• Apheresis for CAR T cell therapy is discouraged within three months of allogenic stem cell transplantation because of risk for GVHD.2

GVHD, graft-versus-host disease; PBMC, peripheral blood mononuclear cell.

Select Considerations Prior to CAR T Cell Infusion

- Premedication with acetaminophen derivatives and antihistamines to reduce the risk of infusion site reactions from CAR T cell therapy\(^1\)
- Prophylactic systemic corticosteroids may interfere with activity of CAR T cell therapy and should be avoided\(^2,3\)
- Access via peripheral or central line for infusion of CAR T cell product, as indicated by each product’s prescribing information\(^4\)
- Washout period between prior therapy (including bridging therapy) and CAR T cell infusion to avoid interference with CAR T cell activity\(^3\)
- CAR T cell therapy should not be administered to patients with active uncontrolled infections or inflammatory disorders\(^5-8\)

Patient Considerations for CAR T Therapy

01 Coordination Between Primary and CAR T Treating Physician

02 Select Considerations Around CAR T Cell Infusion

03 Patient Characteristics and Outcomes

04 Bridging Therapy and Prior Treatment Effects on Patient Outcomes
Factors That May be Associated with Poor Outcomes

- Several baseline factors have been found to be independently associated with risk of relapse after CAR T cell therapy including:
  - Elevated LDH and CRP
  - Low albumin
  - High ferritin
  - Tumor burden
  - Total metabolic tumor volume (TMTV)

- Elevated LDH and CRP, low lymphocyte count, low albumin, and high ferritin have been associated with poor survival following CAR T cell therapy

Characteristics at time of treatment; measured via CT scan; TMTV computed with 41% maximum standardized uptake value threshold method.

CRP, C-reactive protein; LDH, lactate dehydrogenase; TMTV, total metabolic tumor volume.

**Factors That May be Associated with CAR T Cell Toxicity**

Factors that may impact toxicity following CAR T cell therapy may include patient-specific characteristics and/or treatment-related factors

**Factors associated with increased risk for CRS and for neurotoxicity**:  
- Higher CAR T cell doses and lymphodepletion regimens containing fludarabine  
- Higher peak *in vivo* proliferation of CAR T cells  
- Higher disease burden  
- Baseline thrombocytopenia  
- Baseline elevated markers of endothelial activation, including angiopoietin-2 and von Willebrand factor  
- Poor ECOG status (PS 2)

**Factors associated with CRS:**  
- CAR T cells without selection of CD8+ central memory T cells  
- Elevated baseline serum ferritin and CRP

**Factors associated with neurotoxicity:**  
- Elevated CRP after infusion  
- Select serum cytokines and proteins, including: IL-2, sIL-2Rα, IL-6, IL-8, IL-10, IL-15, INF-γ, TNF-α, granzyme B, soluble GM-CSF, and MCP-1

ECOG, Eastern Cooperative Oncology Group; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; PS, performance status; TNF-α, tumor necrosis factor alpha.

*The factors listed here are based on multiple different clinical studies, however research on factors that influence CAR T cell toxicity are ongoing and may vary by disease, specific product, or other factors.*

**References:**  
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Bridging Therapy and Prior Treatment Effects on CAR T Cell Therapy

Various therapies may potentially impact safety and efficacy of CAR T cell therapy

- Prophylactic use of corticosteroids may interfere with activity of CAR T cells
  
- Immunotherapeutic drugs with a longer half-life may interfere with expansion or persistence of infused CAR T cells
  - Eg, alemtuzumab, daratumumab, check point inhibitors, and brentuximab vedotin

- Bridging chemotherapy may contribute to development of cytopenias

Summary

- Evaluation of patients for CAR T cell therapy requires communication and coordination between the primary hematologist and the clinical care team at the CAR T cell therapy treatment site.
- Considerations for CAR T cell therapy include medical history and physical characteristics, as well as socioeconomic factors and caregiver support.
- Prior to apheresis, washout periods may be needed to ensure a sufficient number of cells can be collected for CAR T cell manufacturing.
- Several factors have been found to be associated with risk of relapse and/or poor survival following CAR T cell therapy.
- Select patient-specific characteristics and/or treatment-related factors have been associated with increased risk of toxicity following CAR T cell therapy.
- Certain bridging therapies and prior treatments may affect the safety and/or efficacy of CAR T cell therapy.
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