Long-term Follow-up of Patients Receiving CAR T Cell Therapy

Module 7

The CAR T Academy Modules are intended to provide a high-level overview of select adverse events, and are not meant to be a comprehensive discussion of all adverse events contemplated for CAR T cell therapy.
Patient Journey Through the CAR T Cell Therapy Process

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

2. **Leukapheresis**
   - Patient will undergo apheresis, which involves collection of white blood cells.
   - Collected apheresis product will be sent to the manufacturer for production.

3. **Manufacturing**
   - The CAR T cell product is created at a manufacturing facility.

4. **Prep**
   - Patients may require bridging therapy to maintain disease control while the CAR T cell product is being manufactured.
   - Shortly prior to CAR T cell administration, the patient is prepared for treatment with lymphodepletion.

5. **Treat**
   - The CAR T cell product is delivered to the treatment site.
   - Product is administered.

6. **Monitor**
   - The patient is monitored closely for at least 4 weeks and side effects are promptly managed. Caregiver support is critical during this time.
   - Thereafter, the patient is periodically monitored long term.

Need for Long-term Follow-up

• CAR T cells may persist for multiple years in some patients, underscoring the need for long-term monitoring for late effects of treatment\textsuperscript{1,2}

• Long-term patient monitoring should occur from 30 days through 15 years post-infusion\textsuperscript{3,4}

• Patients should be monitored life-long for the development of secondary malignancies\textsuperscript{5-9}

References:
Transfer Back to the Referring Provider

After at least 4 weeks, or when toxicities resolve, patients can be transferred back to the referring provider.

Recommended Information to Be Shared With the Referring Provider

- Results of all baseline tests performed prior to CAR T cell infusion
- Clinical summary of the patient’s progress, including information regarding the risk for adverse events (AEs) and recommended interventions
- Current disease staging information
- Information regarding specific laboratory orders and how often they should be performed
- Recommendations for monitoring late-onset cytopenias
- Recommendations for possible administration of blood products, if necessary
- Medication list (eg, prophylactic antibiotics and antiviral medications)
- CAR T cell product information (United States Prescribing Information [USPI] and medication guide)
- Copy of patient wallet card listing symptoms that may occur post-treatment
- List of approximate dates when the patient should follow up with the treating center

AEs, adverse events; USPI, United States Prescribing Information.
CAR T Academy: Considerations for Long-term Follow-up

01 Post-treatment Complications

02 Relapse

03 Psychosocial Factors

04 Logistical Considerations

05 Registry
The Physiologic Effects of Post-CAR T Cell Therapy

- The physiologic effects of CAR T cell therapy are becoming better understood as the pool of patients who receive such therapy grows.
- Several interventions can be utilized to address the physiologic effects of CAR T cell therapy, which underscores the need for long-term monitoring to ensure long-term patient safety.

Example Physiologic Effects

- Cytopenias
- Infections
- Fatigue
- Secondary malignancies
- Hypogammaglobulinemia
- Late neurologic toxicities
- Infertility

*Infertility is not a known physiologic effect of commercial CAR T cell therapies.

Cytopenias

Understanding the Risk

• Cytopenias including grade 3/4 anemia, thrombocytopenia, leukopenia, and neutropenia, occur frequently following CAR T cell infusion\(^1\)

• Evidence suggests that CAR T cell therapy can induce myelosuppression via cytokine-mediated and perhaps other mechanisms\(^1\)

• Lymphodepleting chemotherapy administered prior to CAR T cell therapy may also induce myelosuppression\(^1\)

• Cytopenias may persist for long durations\(^2\)
  
  – Cytopenias have been observed in patients up to 24 months following CAR T cell infusion\(^3,4\)
  
  – In a report of patients with NHL, ALL, and CLL (n=86) who received CAR T cell therapy and were followed long term (median duration of follow-up, 28.1 mo; range, 12.5-62.6 mo), 16% (n=3/19 patients with ongoing complete remission) had severe cytopenias lasting beyond 90 days post-infusion (up to 21.7 months)\(^3\)
Cytopenias (cont.)

Monitoring and Follow-up Care

- Monitor blood counts weekly through 60 days post-infusion or as indicated until recovery\(^1\)
- Provide transfusion and/or growth factor support to patients with severe cytopenias, when appropriate.\(^1\) Support may include:
  - Red blood cell transfusions\(^2\)
  - Platelet transfusions\(^2\)
  - Filgrastim\(^2\)

\(!\) Note: Institutional and product guidelines may vary.\(^3\)

ANC, absolute neutrophil count.

Infections

Understanding the Risk

• Immunosuppression is common in patients who receive CAR T cell therapy and may be due to:¹
  – Underlying malignancy
  – Lymphodepleting chemotherapy
  – CAR T cell therapy

• Infections can occur following CAR T cell infusion
  – These may include, but are not limited to: bacteremia, *Salmonella*, urinary tract infections, and viral infections such as influenza, respiratory syncytial virus, herpes zoster virus, Epstein Barr virus, and cytomegalovirus²,³
  – One study demonstrated that ~25% of patients developed infections during first 28 days post-infusion, typically within the first 10 days²
  – Other trials found that 14%-33% of patients developed infections within 30-180 days post-infusion²,⁴,⁵

• Factors that may be associated with increased risk for infection include:²
  – Type of malignancy
  – ≥4 prior lines of therapy
  – Higher CAR T cell dose
  – Higher grade of cytokine release syndrome (CRS)

Monitoring and Follow-up Care

• Closely monitor patients who become febrile after infusion for signs of infection. Keep in mind that fever may also be a sign of CRS\(^1\)

• Since no standard antimicrobial prophylaxis recommendations have been developed for patients who receive CAR T cell therapy, healthcare providers should use their best medical discretion and consider following recommendations for antimicrobial prophylaxis for patients with cancer-related immunosuppression\(^2\)

• No current guidelines exist for revaccination after infusion.\(^3\) Healthcare providers should use their best medical discretion regarding revaccination
  – Consider revaccination ≥6 months after CAR T cell infusion for inactivated vaccines and ≥1 year after infusion for live vaccines, provided the patient is no longer immunocompromised\(^3\)
  – Consider offering flu vaccination ≥30 days post-infusion, particularly in patients who are neutropenic\(^2\)

CRS, cytokine release syndrome

Hypogammaglobulinemia

Understanding the Risk

• B cells produce antibodies that recognize foreign antigens and protect against infection\(^1\)

• CAR T cells can kill healthy B cells in addition to malignant B cells (on-target, off-tumor effect)\(^1\)

• This activity can lead to B-cell aplasia, chronic immunodeficiency, and hypogammaglobulinemia (IgG <400 mg/dL)\(^1\)

• In select clinical trials, hypogammaglobulinemia has been reported to occur in 9%-53% of patients that received CAR T cell therapy\(^2\)-\(^6\)

• Two studies have suggested that ~25%-75% of patients have hypogammaglobulinemia at 30 days post-infusion, up to day 90 and beyond\(^7\)-\(^8\)

• B-cell aplasia and hypogammaglobulinemia can last months to years after treatment and predispose patients to infection\(^1\),\(^9\)

Monitoring and Follow-up Care

• Check immunoglobulin G (IgG) levels monthly\(^10\)

• Consider monthly immunoglobulin infusions for patients who develop frequent infections, especially those with IgG <400 mg/dL\(^1\)

• Given how long this complication can last, IgG replacement may be necessary\(^1\)

Note: Institutional and product guidelines may vary\(^1\)

References:
Secondary Malignancies

Understanding the Risk

- Because genetic alteration is used to create CAR T cells, there is a small possibility that these products can cause insertional mutagenesis, resulting in secondary malignancies. \(^1\)
- In a small cohort of patients followed up to 5.25 years, 15% (n=13/86) \(^2\) developed subsequent malignancies.
- These included nonmelanoma skin cancer, myelodysplastic syndromes (MDS), melanoma, bladder cancer, and multiple myeloma (MM).
- The median time from first infusion to diagnosis for subsequent malignancies was 2 to 16 mo, depending on the type of malignancy.
- No replication-competent lentivirus was detected in CAR T cell products before infusion or in blood samples after CAR T cell infusion.

Monitoring and Follow-up Care

- Healthcare providers need to follow patients who receive CAR T cell therapy life-long for secondary malignancies, per FDA requirements. \(^3\)-\(^8\)
- In the event that a secondary malignancy occurs:
  - Notify the CAR T cell therapy manufacturer. \(^3\)-\(^8\)
  - Report the event to the FDA via MedWatch. \(^4\)-\(^8\)
- Secondary malignancies should be treated per disease-specific protocols. \(^2\)

References:
Late Neurologic Toxicities

Understanding the Risk

- Neurologic toxicities can arise several weeks following infusion, including seizures, weakness, confusion, aphasia, and coordination problems\(^1\)
- In select CAR T cell clinical trials, the incidence of neurotoxicity was 18%-63%\(^a,2-6\)
- In a small cohort of patients followed up to 5.25 years, 10% had neurologic events that occurred 90 days post-infusion or beyond\(^7\)
  - These included stroke, peripheral neuropathy, and dementia

Monitoring and Follow-up Care

- Given the potential for neurologic toxicity, patients should not drive for at least 8 weeks post-infusion\(^1\)
- Seizure prophylaxis (eg, levetiracetam) may be prescribed to prevent seizure\(^1\)
- Patient caregivers should be educated about possible neurologic toxicities and monitor for any changes so they can be immediately addressed\(^1\)

\(^a\)Grading criteria for neurotoxicity varies amongst clinical studies.

Fatigue

Understanding the Risk

• Fatigue can be a common and difficult-to-manage side effect of CAR T cell therapy¹

• In select CAR T cell clinical trials, the incidence of fatigue ranged from 25% to 53%²-⁶

• Fatigue has been reported to resolve in some patients within 4-6 weeks post-infusion¹

Monitoring and Follow-up Care

• Rule out any contributing factors (eg, anemia, hypothyroidism)⁷

• Steroids should be avoided due to potential T cell suppression that might limit the activity of CAR T cell therapy¹

• Nonpharmacologic interventions include exercise, yoga, meditation, Pilates, and massage therapy¹

Infertility

Understanding the Risk

• Effects of CAR T cell therapy on fertility and childbearing outcomes are not yet known\(^1\)

• However, data suggest that lymphodepleting chemotherapy could affect reproductive capacity\(^1\)

Monitoring and Follow-up Care

• Pregnancy and effective contraception should be discussed as part of the treatment plan, particularly for patients who are adolescents or young adults\(^2\)

• Persons of childbearing age should be advised to consult with a fertility preservation specialist prior to lymphodepleting chemotherapy\(^1\)

• Fertility counseling should ideally be scheduled prior to the start of first-line therapy and should continue throughout all lines of treatment\(^1\)

CAR T Academy: Considerations for Long-term Follow-up

01 Post-treatment Complications
02 Relapse
03 Psychosocial Factors
04 Logistical Considerations
05 Registry
Restaging Scans

After a patient undergoes CAR T cell infusion, periodic follow-up is necessary to restage disease and determine the response to treatment.

- Restaging PET/CT scans are typically performed:
  - 30 to 90 days post-infusion
  - Every 3 months for the first 2 years post-infusion

- Reimaging should also be performed for patients with signs/symptoms of disease recurrence (such as unexplained fever or chills, new pain, lymphadenopathy)

Managing Relapse

- Relapse can occur for many reasons\(^1,^2\)
  - Loss of the antigen of interest
  - Lack of persistence or function of CAR T cells
  - CAR T cells may become exhausted, thereby limiting their anticancer effects
  - Tumors can develop compensatory mechanisms that lead to immune evasion
- In certain settings, consolidation therapy with allogeneic stem cell transplantation or participation in a clinical trial (if eligibility criteria are met) can be considered\(^3,^4\)

When relapse occurs, alternative treatment strategies specific to the patient’s disease are necessary (eg, chemotherapy, targeted therapy, clinical trial, etc)\(^4\)

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Psychosocial Effects of CAR T Cell Therapy

Patients may experience:

- Heightened anxiety or fear of recurrence
- Changes in physical functioning that impact quality of life
- Other mental stressors associated with the therapeutic process (e.g., consistent caregiver support, financial concerns) resulting in compromised coping

Survivorship programs are resources that can provide:

- Ongoing communication between patients and treating providers
- Interventions that enable patients to recognize and manage anxiety and that promote positive coping
- Opportunities to engage with other survivors through support groups

Additional avenues of support can include:

- Social workers, chaplains, clinical psychologists/psycho-oncologists, and community-based organizations
- Online forums (eg, social media, online support groups specifically for patients who have received CAR T cell therapy)

Ensuring adequate caregiver support may also prove beneficial

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Logistical Considerations for CAR T Cell Therapy

The total cost of CAR T cell therapy and all medical-related expenses is considerable\textsuperscript{1,2}

- Emergency care or hospitalization for adverse events
- Follow-up appointments for disease and side effects monitoring
- Insurance-related expenses

04: Logistical Considerations

Strategies for Managing Logistics

- Have transparent conversations with patients and caregivers about treatment costs upfront
- Regularly assess for financial constraints and psychosocial sequelae like any other adverse event, and provide support as appropriate
- Connect patients to financial assistance programs

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Patient Registry and Data Capture

• FDA recommends 15 years of observation for patients who receive CAR T cell therapies\(^1\)
• FDA requires REMS programs for commercial CAR T cell therapies\(^2\)

• Center for International Blood and Marrow Transplant Research\(^1\)
  – (CIBMTR) launched a database dedicated to cellular therapy outcomes in 2016
  – Used to capture long-term data for patients who receive CAR T cells or other cellular therapies aside from hematopoietic stem cell transplantation

References:
The CIBMTR Cellular Therapy Registry:

- Offers a platform for standardized, comprehensive data collection
  - After infusion, data captured at 3 months, 6 months, 1 year, and yearly thereafter

- Aligns with FDA regulatory recommendations to capture relevant CAR T cell-associated toxicities
  - Specific outcomes captured include CRS, neurotoxicities, neutrophil and platelet recovery, hypogammaglobulinemia, severe infections, nonhematologic grade 4 toxicities, death from any cause
  - Event-driven forms can be used to report subsequent neoplasms and pregnancies

CIBMTR, Center for International Blood and Marrow Transplant Research; CRS, cytokine release syndrome; FDA, US Food and Drug Administration

Summary

• Several physiologic effects can arise following CAR T cell therapy
  – Many of these may be successfully managed with prophylactic treatment, close monitoring, and prompt intervention, when necessary

• Psychosocial effects and financial constraints associated with CAR T cell therapy should not be overlooked
  – Several avenues of support can help patients cope with these issues, including survivorship programs, support groups, etc

• Periodic imaging is necessary to determine the response to treatment, restage disease, and monitor for relapse
  – When relapse occurs, alternative disease-specific treatment strategies are necessary

• FDA recommends 15 years of observation and long-term AE reporting for patients who receive CAR T cell therapies
  – This can be accomplished by utilizing the CIBMTR Cellular Therapy Registry

AE, adverse event; CIBMTR, Center for International Blood and Marrow Transplant Research; FDA, US Food and Drug Administration.
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