Seminars in Oncology Nursing 37 (2021) 151134

Contents lists available at ScienceDirect

Seminars in Oncology Nursing

journal homepage: https://www.journals.elsevier.com/seminars-in-oncology-nursing

Chimeric Antigen Receptor T-Cell Emergencies: Inpatient Administration, Assessment, and Management

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ARTICLE INFO

Key Words:
Chimeric antigen receptor
Cytokine release syndrome
Neurotoxicity

ABSTRACT

Objective: Chimeric antigen receptor (CAR) T-cell therapy is a genetically modified cellular therapy approved for the treatment of acute lymphocytic leukemia and B-cell lymphoma. This therapy requires patients to remain hospitalized for at least 7 days to monitor for two black-box warnings: cytokine release syndrome and neurotoxicity. Both toxicities require astute monitoring and early treatment to prevent complication.
Data Source: We use a case study to illustrate the assessment and toxicity management of a patient receiving CAR T-cell therapy for diffuse large B-cell lymphoma at an academic medical center.
Conclusion: Cytokine release syndrome and neurotoxicity are two common, potentially life-threatening toxicities that can be reversed with early nursing identification and treatment using evidence-based interventions.
Implications for Nursing Practice: Objective assessment and consensus grading is essential for identification and management of CAR T-cell toxicities.

Background

Chimeric antigen receptor (CAR) therapy is a genetically modified T-cell immunotherapy that uses the body's own immune system to identify and destroy cancerous cells. Using a viral vector, T lymphocytes that have been collected from a patient during leukophoresis are modified to express a receptor that recognizes specific antigens on the surface of malignant cells, causing direct tumor cell death.[1,2] These modified cells are then infused back into the patient following the administration of lympho-depleting chemotherapy and serve as a "living drug" capable of immunologic memory and direct tumor killing.

Currently, CAR T-cell therapy has been approved by the Food & Drug Administration for the treatment of relapsed/refractory CD-19 malignant diseases such as non-Hodgkin's lymphoma and acute lymphoblastic leukemia that have failed two prior lines of systemic therapy.[3,4] The two most common associated side effects include cytokine release syndrome and neurological toxicity.[3,4] Cell manufacturers require close monitoring for at least 7 days to assess for these side effects.

Patient Case Study

S.P. is a 47-year-old male with stage III refractory diffuse large B-cell lymphoma, who was initially diagnosed in April 2020. He received six cycles of D-R-EPOCH, two cycles of R-ICE, and salvage therapy with R-DHAP, none of which induced a remission. Given his refractory disease, he was referred for CAR T-cell therapy with axicabtagene ciloleucel (Yescarta). He was admitted to the inpatient stem cell transplant unit to receive his CAR T-cell infusion, and remained hospitalized for inpatient monitoring of cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS).

Cytokine Release Syndrome

Pathophysiology of CRS

Cytokine release syndrome is the most common toxicity associated with CAR T-cell therapy.[5,6] It is an inflammatory response triggered by myeloid and lymphoid cell lines that produce a rapid release of cytokines.[7] T-cell activation is initiated when it is engaged with the antigens on the surface of malignant B cells. This causes proliferation of the CAR T cells and release of chemokines. These chemokines include IL-6, soluble IL-6 receptor, soluble IL-2 receptor a, interferon gamma, and granulocyte macrophage colony stimulating factor.[8] Other inflammatory markers include C-reactive protein, ferritin, and elevated lactate dehydrogenase.[6]

Clinical Manifestations of CRS

Patients who develop CRS may experience mild flulike symptoms that can progress to life-threatening systemic inflammatory response. It is the most common reaction seen post-CAR T-cell

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https://doi.org/10.1016/j.soncn.2021.151134
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infusion. The severity of symptoms is a direct result of the tumor burden and comorbidities, which correlates with higher T-cell activation.[6,7] The median time onset of CRS ranges from 1 to 3 days, and can occur up to 7 days post-infusion.[3, 4]

Fever is the hallmark sign of cytokine release syndrome.[9,10] Temperatures can exceed 40°C and be accompanied by rigors, malaise, headaches, myalgias, arthralgias, and anorexia.[9] This clinical manifestation is managed by administration of acetaminophen and aggressive cooling measures. It is important to closely monitor patients receiving acetaminophen given the risk for hepatic toxicity. Nonsteroidal anti-inflammatory drugs should not be administered because of their increased risk for hemorrhage, inflammation of the gastrointestinal tract, and renal toxicity.

Hypotension and capillary leak syndrome can also be seen among patients post CAR T-cell therapy, especially among patients having fevers. Also patients can experience cardiac arrhythmias and should be closely monitored given their silent presentation.[5] These clinical manifestations should be managed with conservative fluid replacement given the risk for pulmonary edema and systemic vascular leakage.

Life-threatening symptoms of CRS include uncontrolled fevers, hypotension, and multi-organ failure. Additional clinical manifestations can also be seen among the following organ systems: cardiovascular, pulmonary, renal, hepatic, hematologic, musculoskeletal, neurological, gastrointestinal, and immune. CRS can also cause severe coagulopathy, elevation of urea, compromised urinary filtration, abnormal clotting factors, and hypokalemia.[6,7]

Diagnostic Analysis and Management of CRS

The first step to managing cytokine release syndrome is grading the severity. The American Society of Bone Marrow Transplant (ASTCT) consensus group published an objective universal grading tool. It is categorized based on the severity of the fever, hypoxia, and hypotension (Table 1).

Tocilizumab is the initial pharmacological management for CRS that was approved in August 2017 to induce reversal of IL-6.[8] Symptoms of CRS usually resolve within hours of tocilizumab infusion. Siltuximab is another pharmacological treatment used to manage patients that also blocks the chemokine availability of IL-6. Corticosteroids can also be used to suppress the inflammatory response produced by the chemokines, but are used cautiously because of their direct effects on T cells, which can block the beneficial effects of the CAR T cell.[11] These drugs are reserved for administration when there is no response by the administration of tocilizumab. One of the newest additions to CRS management is anakinra, which blocks the inflammatory activity of IL-1, which is produced by the myeloid cells to downregulate macrophage activity. Anakinra is currently being studied internationally as an additional medication to aid in the prevention and management of CAR T-cell toxicities.[12]

Case Study Application

S.P. developed a fever 2 days after receiving axicabtagene ciloleucel. Blood cultures were collected, antibiotics were started for infection prevention, and acetaminophen was used for supportive measures. He was determined to have grade 1 CRS. He remained febrile with a T_{max} of 39.2°C, and developed profound hypotension systolic blood pressure (SBP = 80) with tachycardia (115 bpm) on day +4. He received multiple fluid boluses, tocilizumab, and dexamethasone. S.P. was also consented to a clinical trial where he would also receive anakinra, an IL-1 antagonist, which was administered subcutaneously for 12 doses. At this time, he met criteria for grade 2 CRS and received aggressive intervention because of his high tumor burden.

By day +5, S.P.'s symptoms began to worsen. He developed pulmonary edema and ascites from aggressive fluid resuscitation and capillary leak syndrome. He was placed on 2 L nasal cannula for increasing oxygen requirements. An arterial blood gas revealed metabolic compensation. His ferritin level peaked at 20,000 ng/mL and his C-reactive protein level ranged from 11.2 to 13.8 mg/dL. At this point, S.P. was experiencing grade 3 CRS and met criteria for intensive care support. He was eventually transferred to the intensive care unit for vasopressor management, and was later intubated for increasing hypoxia. Tocilizumab, dexamethasone, and anakinra were continued for CRS management.

On day +8, he was extubated and his blood pressure remained stable after the discontinuation of vasopressors. He remained afebrile, and showed no additional signs of CRS. The critical care team prepared to transfer him back to the stem cell transplant unit to continue close monitoring. However, later that day the patient was noted as disoriented and was unable to write a sentence as part of the Immune Effector Cell Encephalopathy (ICE) assessment.

Immune Effector Cell-Associated Neurotoxicity Syndrome

Pathophysiology of ICANS

Neurological toxicity (also known as immune effector cell-associated neurotoxicity syndrome [ICANS]) is the second major side effect that has the potential to develop following CAR T-cell therapy. This toxicity can be subtle and develop into a life-threatening condition. The pathogenesis is less clear, however, it is known to peak during the in vivo numbers of circulating CAR T-cells.[8] Those with high levels of C-reactive protein and early peak of IL-6 have been associated with severe neurological toxicity.

Neurological toxicity has also been seen in patients who have elevated cerebrospinal fluid protein levels indicating that CAR T cells have crossed the blood–brain barrier during proliferation and expansion.[2,8] Patients who experience ICANS often have specific factors that increase their risk, such as the type of disease, tumor burden, chemotherapy treatments prior to infusion, and their age.[8]

Clinical Manifestations of ICANS

Clinical manifestations of neurological toxicity include confusion, delirium, expressive aphasia, weakness of the extremities, tremors,

Table 1
ASTCT CRS Grading Criteria[10]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temp ≥ 38°	Temp ≥ 38°	Temp ≥ 38°	Temp ≥ 38°
Hypotension	None	With Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requires multiple vasopressors
Hypoxia	None	And/or Requires low-flow nasal cannula (6 L/min or less) or blow-by	Requires high-flow nasal cannula (>6 L/min), face mask, non-rebreather, or Venturi mask	Requires positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Abbreviations: CPAP, stands for continous positive airway pressure; BiPAP, stands for bilevel positive airway pressure.
* If patient is receiving anticytokine or antipyretic therapy, CRS grading is driven by hypotension and/or hypoxia.

TABLE 2
ICE Assessment Tool[10]

ICE Assessment Tool		
Orientation	Patient is oriented to year, month, city, hospital	4 points
Naming	Patient is able to name 3 objects in room (eg, point to clock, pen, cup)	3 points
Following Commands	Patient is able to follow a simple command (eg, hold up 2 fingers; close your eyes and stick out your tongue)	1 point
Writing	Patient is able to write a standard sentence (eg, "Our national bird is the bald eagle.")	1 point

seizures, decreased level of consciousness, and inflammation of the brain.[8] These symptoms appear 1 to 3 weeks after CAR T-cell infusion and usually correlate with the onset of CRS.[3,4,13] Patients may also exhibit changes in their ability to pay attention, process verbal stimuli, name objects, and/or write a sentence. Severe symptoms can include cerebral edema, hemorrhage, or paralysis, and may require intensive care support for airway management. In most cases, symptoms are transient and usually reverse in 4 weeks without any long-term deficits.[2,6]

Diagnostic Analysis of ICANS

The American Society of Bone Marrow Transplant (ASTCT) consensus guidelines published a new universal tool used to grade neurological toxicity.[10] The ICE score provides an objective score for evaluation of neurologic toxicity in adults based on the patient's ability to follow certain commands and evaluate alterations in speech, orientation, and handwriting (Table 2).

Grading of neurological toxicity is determined by the most severe clinical finding that is not attributed to any other cause (Table 3).

Management of ICANS

ICANS management is guided by severity and grading. Mild neurotoxicity (grade 1–2) can be managed with supportive care, neurology consultation, and diagnostic testing to rule out other clinical findings (eg, CT scan, MRI, and EEG). Seizure prophylaxis may be considered in patients who are at higher risk.[6,13]

Tocilizumab is the primary treatment for managing patients who experience neurological toxicity concurrently with CRS. However, for neurotoxicity that occurs in the absences of CRS, corticosteroids are considered first-line treatment.[14] Steroids are indicated in the management of ICANS because of their ability to cross the blood–brain barrier.[11] Patients who experience higher grades of ICANS (grade 3–4) may require intensive care for intubation and airway protection.[14]

Case Study Application

The transfer back to the stem cell transplant unit was cancelled because of the onset of grade 2 ICANS, and the patient remained in the intensive care unit for close monitoring and a neurology consultation. Diagnostic imagining included an MRI and EEG, which was consistent with encephalopathy. Anti-epilectics and seizure precautions were initiated, and S.P. was restarted on dexamethasone for worsening neurotoxicity. He continued to receive anakinra as part of a clinical trial.[12] Neurologic checks and ICE assessments were performed frequently, and his ICANS symptoms eventually resolved on day +16. He returned to the stem cell transplant unit for physical therapy and *Clostridium difficile* management while his blood cell counts recovered.

Prolonged Cytopenia and Risk for Viral Reactivation Following CAR T-Cell Infusion

Patients who receive CAR T-cell therapy are at risk for anemia, neutropenia, and thrombocytopenia. Frequent blood count monitoring and transfusion support may be necessary in the weeks following lymphodepletion.[2,4] Bacterial, viral, and fungal infections have occurred in patients following CAR T-cell infusion. Patients should be monitored closely for signs and symptoms of infection, and treated with prophylactic coverage per institutional guidelines. Recovery of blood cell counts should occur within 30 days of infusion.[2,4]

Because CAR T cells are targeted to destroy cells that express CD19, healthy B cells can also be affected.[2,4,6] The longevity and persistence of the CAR T cell can lead to B-cell aplasia, hypogammaglobulinemia, and increased risk for infection and viral reactivation. Immunoglobulins should be monitored, and intravenous immunoglobuline may be required for passive replacement until B cell function has been restored.[2,6] Patients who experience high grades of CRS and/or ICANS may also have delayed hematopoietic recovery[15] and should be monitored closely for signs of infection.

Case Study Application

After recovering from CRS and ICANS, S.P. remained neutropenic with an absolute neutrophil count of $0.05 \times 10^3/\mu$l. On day +17, he reported mouth dryness and pain. An oral mucosal ulcer was discovered on exam and a culture was sent to rule out infectious etiology. S. P. was found to have a herpes simplex virus reactivation, and was started on acyclovir. His *C. difficile* infection was treated with vancomycin and fidaxomicin. He continued to have persistent neutropenia and was started on filgrastrim to stimulate white blood cell recovery. He remained in the hospital until his neutrophil count recovered on day +30.

TABLE 3
ASTCT ICANS Consensus Grading for Adults[10]

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score for patients aged 12 and older	7–9	3–6	0–2	0 (patient unarousable or unable to perform ICE)
Depressed level of consciousness	Awakes spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electoral seizure without return to baseline in between
Motor Findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decoriticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Implications for Oncology Nursing

CAR T-cell therapy is an emerging immunotherapy that is now approved for commercial use in non-Hodgkin lymphoma and acute lymphoblastic leukemia. As more CARs are being developed for other targets and diseases, objective assessment using consensus grading will be essential for identification of toxicities. Early recognition and grading can aid oncology nurses in selecting evidence-based interventions to manage and reverse potentially life-threatening side effects. Nurses should utilize these objective assessments and grading criteria as part of their daily management, especially when neurotoxicity is suspected, and changes in patient status can be subtle.

S.P. was eventually returned home without any long-lasting effects from the CAR T-cell toxicities he experienced while in the hospital. On follow-up with his oncologist, he had no evidence of disease on a repeat bone marrow biopsy and PET scan. Because of the astute and timely assessments and early intervention by the health care team, S.P. was able to finally achieve a remission.

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