Cytokine Release Syndrome

Inpatient care for side effects of CAR T-cell therapy

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BACKGROUND: Pediatric patients with relapsed and refractory acute lymphoblastic leukemia are more often being treated with chimeric antigen receptor (CAR) T-cell therapy. As with any new therapy, the management of this patient population has a unique set of challenges. The side effects of this therapy can range from mild to severe, with cytokine release syndrome being the most common reason for hospitalization.

OBJECTIVES: This article presents common side effects, treatments, and challenges of caring for hospitalized patients who have received CAR T-cell therapy.

METHODS: A case study is used to illustrate a patient’s inpatient hospitalization course after receiving CAR T-cell therapy, including the management of treatment-related toxicities.

FINDINGS: As treatments emerge, nurses will be challenged with learning the associated side effects and toxicities. CAR T-cell therapy can result in a unique trajectory of potential symptoms and the potential for complete resolution of disease.

KEYWORDS
- cytokine release syndrome
- CAR T-cell therapy
- pediatric patients
- immunotherapy

DIGITAL OBJECT IDENTIFIER
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CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY is being used more often for pediatric patients with relapsed and refractory acute lymphoblastic leukemia (ALL). As with any new therapy, CAR T-cell therapy comes with a unique set of challenges for symptom management. Side effects can range from mild to severe. Mild side effects can be managed in an outpatient setting, and severe events with multisystem organ failure may require care in an intensive care unit (ICU). The primary complications of CAR T-cell therapy are well documented and include cytokine release syndrome (CRS), neurologic symptoms, tumor lysis syndrome, and graft-versus-host disease (GVHD), each of which may require hospitalization for symptom management (see Table 1). As frontline providers, nurses are often first to identify the signs and symptoms of complications and acute changes in a patient’s status. Understanding the hallmark complications, signs, symptoms, and management of these common complications can better prepare nurses to deliver safe and effective care in the clinical setting. This article uses a case study to address inpatient management of the moderate to severe toxicities that are specifically related to CAR T-cell therapy.

Case Study
D.M. is a 21-year-old man who was initially diagnosed in 2001 with ALL at age six years. Ten months after therapy, he experienced his first relapse, was treated, and achieved remission again. He developed his second relapse four years off therapy, after which he was not able to achieve chemotherapy-induced remission. Prior to receiving CAR T-cell therapy targeting the CD19 antigen (CART-19), his bone marrow had 93% blasts, and his minimal residual disease was 68%. He received the T-cell infusions without incident in the outpatient clinic. Information about the infusion process is outlined in this supplement by Callahan, Baniewicz, and Ely (2017). After he received the infusion, his family was educated on symptoms that would require inpatient medical interventions, and he was sent home with instructions for a follow-up appointment and 24/7 contact information for the team.

Cytokine Release Syndrome
CRS is a constellation of symptoms that occur when T cells engage and begin to proliferate in the body and lead to a general inflammatory response. It is the main complication requiring hospitalization after CAR T-cell therapy...
(Maude, Barrett, Teachey, & Grupp, 2014). In the context of CRS, a dramatic increase in interleukin-6 (IL-6) is observed, along with elevations of other cytokines (e.g., IL-10). Other markers of CRS include elevated lactate dehydrogenase, C-reactive protein (CRP), and ferritin. A rise in CRP is an early indicator of the inflammatory process, but ferritin tends to rise more slowly. Although these are not absolute predictors of how severe the CRS will be, they can help predict how long the patient’s inflammatory course may persist. The severity of CRS appears to be related to the disease burden prior to CAR T-cell therapy (Maude, Shpall, & Grupp, 2014; Singh, Frey, Grupp, & Maude, 2016; Maude, Teachey, Porter, & Grupp, 2015; Teachey et al., 2016). A higher disease burden correlates with a greater risk for developing more severe CRS.

Symptoms
In CRS, fevers can range from low (38°C) to high (40°C) grade and can persist for days to weeks. Acetaminophen is used for comfort but frequently does not relieve the fever. With fevers, patients often experience fever-associated tachycardia and chills. Many children also develop anorexia, nausea, and vomiting that require supportive care, such as antiemetics and IV nutrition. Of note, nausea and anorexia tend to last for weeks after other symptoms of CRS have subsided. Many children also develop myalgia and headaches, requiring intermittent IV opioids or patient-controlled IV opioid infusions. These symptoms can appear as early as one day after infusion. They can have a relatively short duration or be prolonged, lasting for weeks.

More severe symptoms of CRS include capillary leak syndrome and hypotension. With the inflammation that results from CRS, hyperpermeability of capillaries allows for fluid to leak from blood vessels into third spaces, such as lung and interstitial tissues, which can lead to intravascular depletion. This intravascular depletion can lead to or worsen existing hypotension. Because of capillary leak syndrome and the interventions used to treat hypotension, these side effects can lead to pulmonary edema and the need for oxygen support. Respiratory support ranges from nasal cannula supplementation to intubation. Treatment for hypotension always starts with IV fluid boluses, but healthcare providers should quickly move toward vasopressor support to minimize the risk of massive pulmonary edema. In the current authors’ institution, once a second IV fluid bolus is required, the critical care team is consulted, with the intent to have patients transferred proactively to the ICU to avoid emergency situations on the floor. Hypotension and capillary leak syndrome tend to appear four to seven days after infusion (Maude, Frey, et al., 2014; Singh et al., 2016; Teachey et al., 2016).

CRS can also lead to severe coagulopathy, with prolonged prothrombin time (PT), partial thromboplastin time (PTT), and low fibrinogen levels (Maude, Frey, et al. 2014). The authors’ institution has also observed increased D-dimers; however, this could be reflective of inflammation rather than disseminated intravascular coagulation. Treatment includes transfusions with cryoprecipitate to maintain a fibrinogen level greater than 150 mg/dl. Fresh frozen plasma is given as clinically indicated for prolonged PT/PTT and bleeding. Patients are also transfused to maintain a platelet threshold greater than 20,000. The threshold is raised if there are concerns of bleeding. Although patients may experience abnormal coagulation, severe bleeding is uncommon (Maude, Frey, et al., 2014).

The inflammation from CRS causes changes in hemodynamics, initiating a decrease in renal blood flow and subsequent decrease in glomerular filtration rate. As a result, acute kidney injury and renal dysfunction can occur after CAR T-cell infusion. Renal

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>SYMPTOM</th>
<th>TREATMENT</th>
<th>NURSING ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>Fever, myalgia, headache, anorexia, nausea and vomiting, renal dysfunction, coagulopathy, hypotension, capillary leak, and pulmonary edema</td>
<td>Acetaminophen, narcotics, total parenteral nutrition, antiemetics, renal dosing of medications to dialysis, fresh frozen plasma, cryoprecipitate, platelets, vasoactives, tocilizumab, methylprednisolone, oxygen support, and intubation</td>
<td>Take vital signs every four hours. Do daily laboratory tests of electrolytes, hepatic function, coagulation factors, C-reactive protein, lactate dehydrogenase, and ferritin. Obtain daily weights.</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td>Rash, diarrhea, and hyperbilirubinemia</td>
<td>Topical triamcinolone, possible systemic treatments with calcineurin inhibitors or steroids (only in discussion with CAR T-cell therapy team)</td>
<td>Skin assessment and output assessment. Neurologic examinations</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>Confusion, B-cell aphasia, unresponsiveness, and seizures</td>
<td>Supportive care (e.g., reorientation, antiepileptics)</td>
<td>Neurologic examinations</td>
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<tr>
<td>Tumor lysis syndrome</td>
<td>Hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia</td>
<td>Allopurinol and hydration</td>
<td>Daily electrolytes</td>
</tr>
</tbody>
</table>

CAR—chimeric antigen receptor

TABLE 1.
COMMON SIDE EFFECTS OF CAR T-CELL THERAPY AND THEIR TREATMENT
dysfunction can be mild (e.g., slight elevation in creatinine, causing difficulty clearing medications) to severe (e.g., elevations reflecting renal failure, possibly requiring hemodialysis). Increased cytokine production can also have direct actions and cause injury to glomerular cells (Maude, Frey, et al., 2014).

Some patients experiencing severe CRS have also developed macrophage-activation syndrome or hemophagocytic lymphohistiocytosis. Symptoms include prolonged sustained high fevers; hepatosplenomegaly; severe coagulopathies; and high ferritin, triglycerides, and transaminases (Grupp, 2014; Maude, Frey, et al., 2014).

**Treatment**

CRS is a reversible inflammatory process. The goal in treating CRS is to control symptoms without interfering with the efficacy of T cells. This requires a fine balance of providing symptom management while preserving the function of the CAR T cells. CRS is a group of inflammatory symptoms caused by the CAR T cells proliferating and destroying the CD19-positive malignant cells. Treatments that suppress inflammation may also interfere with the ‘T cells’ ability to destroy the malignant cells. However, not treating these symptoms could lead to multisystem organ failure and death. First-line treatment is always aimed at supportive care, such as use of antipyretics, pain medications, antiemetics, vasopressor support, and oxygen supplementation. As patients appear to develop multisystem organ failure, other medications are considered.

**TOCILIZUMAB**

Tocilizumab (Actemra®) is a humanized monoclonal antibody that targets the IL-6 receptor. It binds to the receptor, preventing IL-6 from binding and causing inflammation. Because it does not directly affect the T cell, it is believed that it may not have long-term effects on T-cell efficacy. Tocilizumab is very well tolerated but, in rare cases, may cause transaminitis (elevated liver transaminases) and neutropenia. Because it is a monoclonal antibody, patients are premedicated with acetaminophen and diphenhydramine (Benadryl®) prior to the infusion. Tocilizumab tends to quickly resolve symptoms, with fevers resolving within 24–48 hours, and restores normal levels of oxygen and blood pressure issues shortly thereafter. Clinical indications for administering tocilizumab include hypotension, requiring the addition of a second blood pressure medication, or worsening respiratory status (e.g., increased rate, work of breathing, hypoxia) that could lead to intubation (Barrett, Teachey, & Grupp, 2014; Maude, Frey, et al., 2014; Maude et al., 2015).

**METHYLPREDNISOLONE**

Methyprednisolone (Medrol®) works by directly blocking the activation of T cells and, therefore, decreasing inflammation. Because it directly affects T cells, it may also stop the beneficial effects of the CAR T cells. At this time, methylprednisolone is given only if other interventions, including tocilizumab, are unsuccessful.

**CLINICAL OUTCOMES**

At the authors’ institution, 53 of 59 patients developed some level of CRS. In 22 of those cases, patients required tocilizumab for either hemodynamic or respiratory instability (Maude et al., 2015). Ten patients also required methylprednisolone. All cases of CRS have been reversible. Two of the patients who received therapies to suppress CRS relapsed, but it is unclear whether the relapse was directly caused by the use of these medications (Barrett et al., 2014; Maude, Frey, et al., 2014; Maude et al., 2015).

**CASE STUDY APPLICATION**

D.M. developed fevers the day after his infusion and was admitted to the hospital for antibiotics and observation. He remained persistently febrile, with a maximum temperature of 39.7°C. He developed full-body myalgia and headaches on admission, requiring patient-controlled IV opioid infusion. On day five postinfusion, he became profoundly hypotensive (blood pressure ranging from 40/20–50/20), necessitating the administration of multiple IV fluid boluses and blood products. At this time, the critical care assessment team was consulted, and D.M. was transferred to the ICU for vasopressor therapy with norepinephrine (Levophed®), dopamine, and vasopressin. The fluid boluses led to pulmonary edema and intubation. At that time, his inflammatory markers showed peak CRP of 34 mg/dl (normal range = 0–0.9 mg/dl), ferritin of 3,980 ng/ml (normal range = 10–358 ng/ml), and D-dimer of greater than 5 mcg/mlFEU (normal range = 0.27–0.6 mcg/mlFEU). He received tocilizumab and had some improvement of symptoms. By day seven postinfusion, he was weaned off vasopressin and norepinephrine and was extubated to high-flow oxygen via nasal cannula. At that time, his coagulation factors showed fibrinogen of 102 mg/dl, PT of 34 mg/dl (normal range = 0–0.9 mg/dl), ferritin of 3,980 ng/ml, and D-dimer of greater than 5 mcg/mlFEU. He was transfused with fresh frozen plasma but did not have any clinically significant bleeding. On day eight postinfusion, he became hypotensive again (blood pressure in the 70s/40s), requiring increasing blood pressure support. At this time, a second dose of tocilizumab was given (inflammatory markers showed CRP of 6.6 mg/dl and ferritin of 23,500 ng/ml). By day nine, he was stable and off oxygen support, and, by day 10, he was off blood pressure support. From days 9–13, he remained coagulopathic, receiving multiple cryoprecipitate and plasma transfusions to prevent bleeding events. Recovery from ICU level of care occurred over 11 days, with eventual transfer back to the oncology unit.

**Neurologic Symptoms**

A unique set of neurologic symptoms can occur with CAR T-cell therapy. CAR T cells have been found in the cerebral spinal fluid regardless of central nervous system (CNS) disease (Maus, Grupp,
Several patients have developed a distinct encephalopathy that tends to be quick in onset but relatively short in duration. The most common symptoms experienced are confusion, hallucination, and delirium. A few have developed expressive aphasia. In a severe case, a patient with high CNS burden became unresponsive for several days. No interventions exist to reverse encephalopathy, but it can resolve independent of treatment. In all cases, encephalopathy resolved without long-term effects. For the first several patients experiencing encephalopathy, diagnostic tests, such as computed tomography scans and magnetic resonance imaging, and lumbar punctures were performed and did not identify any abnormalities (Maude et al., 2015). Several patients, primarily those with a history of seizure activity, have also developed seizures. All patients who are thought to be at risk for seizures are started on prophylactic levetiracetam (Keppra®) at the start of CRS and continue on it until all symptoms of CRS are resolved (Maude, Frey, et al. 2014; Singh et al., 2016).

Case Study Application
D.M. developed intermittent confusion and aphasia on day eight. These symptoms included expressive aphasia and slurred speech. Monitoring included frequent neurologic checks and reorientation to time and place. His symptoms also included expressive aphasia and slurred speech. Monitoring included frequent neurologic checks and reorientation to time and place. These symptoms lasted until day 16, when they completely resolved.

B-Cell Aplasia
CART-19 therapy targets any cells expressing the CD-19 antigen, which includes normal B cells; therefore, patients who receive and respond to CART-19 therapy develop B-cell aplasia. The goal is for the CAR T cells to persist, resulting in B-cell aplasia. B-cell aplasia leads to hypogammaglobulinemia because B cells produce immunoglobulins. Immunoglobulins have an important role in the immune system because they recognize foreign antigens and trigger the immune system to eliminate them. Immunoglobulin G (IgG) is the most abundant, comprising 75%–80% of all immunoglobulins. To prevent risk of infection because of lack of IgG, patients receive monthly IV immunoglobulin infusions to maintain an IgG level greater than 500 mg/dl. As long as B-cell aplasia occurs, IV immunoglobulin should be given regardless of the level (Maude, Shpall, et al., 2014; Maude et al., 2015).

Tumor Lysis Syndrome
Tumor lysis syndrome occurs with the rapid death of leukemia cells, causing hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which can lead to acute renal failure if untreated. This is a concern for any patient presenting with a high tumor burden prior to CAR T-cell therapy. Many patients are treated with allopurinol (Zyloprim®), but all patients have daily monitoring of uric acid and electrolytes, with treatment as indicated. This has not been a major problem for any patient under treatment in the authors’ center (Barrett, Singh, Porter, Grupp, & June, 2014; Grupp, 2014).

“A higher disease burden correlates with a greater risk for developing more severe cytokine release syndrome.”

Graft-Versus-Host Disease
GVHD occurs when the graft (donated lymphocytes) recognizes the host (the patient) as foreign, causing an immunologic response. The most common target organs of GVHD are the skin (causing rash), the gastrointestinal tract (causing diarrhea), and the liver (causing hyperbilirubinemia). Historically observed in allogeneic stem cell transplantation recipients, GVHD is a concern for any patient undergoing CAR T-cell therapy who has had a previous stem cell transplantation. The T cells that are collected from these patients may be donor-derived. Because activated donor T cells, such as CAR T cells, can cause GVHD, patients who have undergone stem cell transplantation may experience GVHD. The other concern is that mainstay treatment for GVHD is methyprednisolone, which is contraindicated because of the effect on T-cell proliferation. To date, no patient at the authors’ center has developed GVHD after CAR T-cell therapy.

Hospital Discharge Criteria
Discharge criteria after admission for management of CAR T-cell therapy toxicities include being afebrile for at least 24 hours, twice weekly or fewer transfusion requirements, and the ability to maintain adequate hydration. Prior to discharge, patients with severe CRS are screened by physical therapists to ensure that they are safe to leave the hospital. With complicated courses, some patients have required an inpatient rehabilitation stay because of severe deconditioning. If the patient is neutropenic at the time of discharge, they receive oral levofloxacin (Levaquin®) prophylaxis to take after discharge. Consideration should be given to the coordination of care and supplies, particularly for patients traveling long distances for treatment. Ensuring insurance coverage for medications, supplies, and any home-based therapies should be done early in the admission process. In many instances, the outpatient team proactively collaborates with the referring institutions to ensure...
that patients have a six-week supply of homecare equipment and medications, such as levofloxacin and antifungals. Because many patients remain neutropenic upon discharge, families are re-educated on the importance of infection prevention and recognizing signs that would require medical intervention. Patients continue to follow up in the outpatient clinic twice weekly until they are able to return back to their home institutions.

**Psychosocial Care**

Psychosocial care is integral to the holistic care of pediatric patients and their families (Callahan et al., 2017). On admission at the authors’ institute, all children are assigned a child life specialist (CLS) to help with coping mechanisms and to adjust to their new environment, and a social worker to assist in navigating the treatment process. Having a designated primary social worker and CLS provides consistency in planning care, facilitates consistent communication, and helps build trust in the team as the relationship develops. Art and music therapy are also available to those interested or those identified as having difficulty coping by their CLS or social worker. Engaging multidisciplinary team members, as highlighted by Callahan et al. (2017), can offer holistic psychosocial care to pediatric patients, who are vulnerable during new and novel treatment with CAR T-cell therapy, and their caregivers.

A unique observation in CAR T-cell therapy is the patient’s or caregiver’s perception of a proportional relationship between the severity of sequelae, such as CRS, and the efficacy of the treatment. Although the degree of CRS is directly related to disease status prior to infusion, it appears to not be directly related to antitumor effect (Maude et al., 2015; Maus et al., 2014). The team needs to provide reassurance that, although the child does not develop severe CRS, they may still benefit from CAR T-cell therapy.

The psychosocial care of these patients and families is just as important and complex as the medical care during this treatment. Some patients and families have been in the medical system for many years, often dealing with multiple relapses. After spending many years in the medical world, families have gained support and built relationships with their primary oncology team. These families are then required to leave the comfort of these relationships and be introduced to a new medical and support team. Often, they leave their homes and travel to another state, leaving behind their established social network. They are required to stay in the coordinating infusion center area for six weeks after CAR T-cell therapy. Institutional policy for routine care (e.g., central line dressing change and access) may differ across hospitals, causing confusion for families who have been providing care to their child for many years. Aside from the stress of multiple relapsed leukemia, they also need to adapt to the change of processes and procedures. To help alleviate this stress at the authors’ institution, families are provided with written materials of how common procedures, such as central line care and nasogastric tube care, are performed for them to be prepared for the potential change in practice. Healthcare providers stress that one method is not necessarily better than another but that consistency in staff practice for repeated procedures leads to the safest patient outcome and decreases patient stress.

**Conclusion**

CAR T-cell therapy is one of many new and emerging immunotherapy treatments for diverse cancer types. As these treatments continue to emerge, nurses will be challenged with learning the many side effects and toxicities associated with these treatments. Using evidence-based resources to guide the assessment, identification, and management of such complications is critical to providing safe and effective care to patients with cancer. In the context of CAR T-cell therapy, being knowledgeable of the causes, symptoms, and clinical management of CRS, neurologic toxicities, GVHD, tumor lysis syndrome, and B-cell aplasia can enhance nurses’ clinical practice and care provision to this population. Ultimately, immunotherapies, such as CAR T-cell therapy, result in a unique trajectory of potential symptoms and the potential for complete resolution of disease. In the case study, D.M. was able to return home with no evidence of disease after a bone marrow aspiration on day 28. Holistic care during and after treatment, along with a multidisciplinary approach to care coordination among ambulatory, inpatient, and community settings, can enhance the experience of pediatric patients and their caregivers.
REFERENCES