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Chimeric Antigen Receptor T Cell Therapy and the Kidney

What the Nephrologist Needs to Know

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Introduction

T cells are critical in orchestrating the immune response and killing cells infected by pathogens. In 1989, Gross *et al.* (1) reported the experiments introducing the genetic code for an antibody recognition site into a cytotoxic T cell that imparted the ability to recognize a specific antigen. Twenty-five years later, a breakthrough in technology has allowed us the ability to construct T cell receptors with antitumor specificity, allowing clinicians the ability to harness the immune response against cancer (2). This rapidly emerging form of immunotherapy is called adoptive cell transfer. This allows for collecting and using a patient's own immune cells to treat his/her cancer. Chimeric antigen receptor T (CAR-T) cell therapy is the first US Food and Drug Administration (FDA)–approved (2017) adaptive cell transfer treatment indicated for patients ages 3–25 years old with relapsed or refractory acute lymphoblastic leukemia (ALL) (3). This therapy requires drawing of blood from patients and separating out T cells. After that, using a disarmed virus, the T cells are genetically engineered to produce receptors on their surfaces called chimeric antigen receptors. These synthetic receptors allow the T cells to recognize and attach to a specific protein: in this case, a tumor antigen. These engineered T cells are expanded into hundreds of millions in a cell manufacturing facility. Finally, the CAR-T cells are infused into the patient (preceded by a lymphodepleting chemotherapy regimen). These CAR-T cells can then selectively target and kill cells expressing the tumor antigen (Figure 1) (2).

The initial development of CAR-T cell therapies has been focused largely on ALL (3), the most common cancer in children. The early success of this therapy was in CD-19–targeted CAR-T cell therapy called tisagenlecleucel (Kymriah) for children and adolescents with ALL. CD-19 is a surface protein found on B cells. Also, later in 2017, the FDA approved another CD-19–targeted CAR-T cell therapy called axicabtagene ciloleucel (Yescarta) to treat adults with certain types of large B cell lymphoma. Currently, CAR-T cell therapies have been largely focused on hematologic malignancies, but they are also being

studied in solid cancers, such as glioblastoma multiforme, ovarian cancer, pancreatic cancer, mesothelioma, and prostate cancer (4–6). Given the proliferation of these therapies, it is important for nephrologists to understand the potential kidney effects that may be encountered in these patients.

Nephrotoxicities Associated with CAR-T Cell Therapy

Cytokine Release Syndrome

In all published trials of CD-19–directed CAR-T cells, cytokine release syndrome was observed in >40% of the patients, regardless of the disease studied or the construct of the CAR-T cells (4–7). In a recent large retrospective evaluation of patients with ALL receiving CAR-T cell therapy, 46% developed cytokine release syndrome (8). In spite of pretreatment for this condition, this is still a common and potentially serious complication of which nephrologists to be aware. These patients present initially with fevers for 6–7 days and often have rising ferritin levels. Organ dysfunction is manifested on days 14 and 15 for most patients. Over 25% of the patients can develop cardiac dysfunction, leading to a shock-like state as well. This syndrome is due to high levels of a multitude of circulating inflammatory cytokines, predominantly IL-6 (8). Cytokines are produced either directly by CAR-T cells or by the immune cells activated by the CAR-T cells. Diagnostic criteria used for cytokine release syndrome diagnosis include fevers for at least 3 consecutive days; C-reactive protein ≥20 mg/dl; at least one clinical sign of toxicity, such as hypotension requiring pressor support; hypoxia (oxygen saturation <90%); and neurologic changes (mental status changes, seizures, and obtundation) (8). In some trials of CAR-T cells, the severity of cytokine release syndrome has been correlated with the extent of baseline hematologic disease. Cytokine release syndrome can manifest in specific organ systems, including the kidneys. The release of high concentrations of cytokines can lead to vasodilation, decreased cardiac output, and intravascular volume depletion due to increased vascular permeability and third spacing of fluids, causing reduced perfusion to the kidneys and AKI. The rise in serum creatinine is noted at approximately days 7–10 postinfusion (4,7,8). Prerenal AKI and/or acute tubular injury may develop in this setting depending on the severity of hypotension and its duration (Figure 1). Furthermore, cytokine release syndrome–related cardiomyopathy can also lead to a shock state and acute cardiorenal syndrome with concomitant AKI. Cytokines themselves may potentiate the renal injury due to intrarenal inflammation. Accumulation of fluid in the interstitial space leads to other challenges, such as pleural effusions, peripheral edema, pulmonary edema, intestinal edema, ascites, and muscle edema. Rarely, AKI can result from severe ascites, and the development of compartment syndrome and/or muscle edema induced rhabdomyolysis (Figure 1).

Mild to moderate cytokine release syndrome is most often treated with supportive care, with close monitoring of organ function and organ-specific interventions as needed. Intensive care admission is critical for many patients with this syndrome to allow for close monitoring. Although volume resuscitation improves BP and kidney function, edema can worsen, and vasopressor support is often prudent to avoid volume overload. Loop diuretics, possibly with 25% albumin, might also be required in some patients to help mobilize edema. Rarely, RRT may be indicated for the usual indications. For patients with more severe cases (typically manifesting as hypotension and/or hypoxia), anticytokine therapy with tocilizumab (human mAb against the IL-6 receptor) has been very effective in quickly reversing the cytokine storm in most patients (9). This was on the basis of the observation that IL-6 was among the most elevated cytokines in severe cytokine release syndrome. Tocilizumab is now considered standard of care therapy for severe cytokine release syndrome and can be given with or without corticosteroids. The effectiveness of other IL-6–directed therapies, such as siltuximab, is not well established, but they could be considered as second-line treatment in cytokine release syndrome management (9). Methylprednisolone 1–2 mg/kg intravenous every 12 hours can be tried in cytokine release syndrome that is refractory to tocilizumab (9). Pretreatment with chemotherapy to reduce tumor burden and steroids is also considered to be important in the prevention of cytokine release syndrome (8,9). Another syndrome along the spectrum of cytokine release syndrome that can be associated with AKI is hemophagocytic lymphohistiocytosis or macrophage

activation syndrome, which is thought to be at least partially related to elevations of IL-6 and IL-10 (9,10). To help guide treatment, recent workgroup guidelines in grading and management of CAR-T cell–related toxicities were established (10).

Tumor Lysis Syndrome

In the initial trials of CAR-T cell therapy, findings of tumor lysis syndrome have been noted (3,4). When used for treatment of chronic lymphocytic leukemia, Porter *et al.* (4) noted an elevation in uric acid and lactate dehydrogenase on or about 22 days after CAR-T cell infusion. Phosphorus levels were not significantly elevated but were in the 4- to 4.7-mg/dl range, and AKI was noted. In trials of CAR-T cells with ALL, mild elevations of lactate dehydrogenase and slightly elevated levels of uric acid were noted. Most patients who were at risk for tumor lysis syndrome did receive allopurinol on days 0–14 of therapy. Although thus far, patients with mild cases of tumor lysis syndrome have been reported, severe cases in patients leading to potential AKI remain a possibility.

Electrolyte Disorders

In the initial trials of using CAR-T cells for ALL, electrolyte disorders were reported. The most common was hypokalemia (47%), which was followed by hypophosphatemia (37%) and finally, hyponatremia (5%) (10). It is unclear if this is related to CAR-T cell therapy directly or a result of cytokine release syndrome. Mechanisms of the electrolyte disorders are unclear; however, vigilance in monitoring is critical, and standard treatment protocols should be used.

Conclusions

The approval of CAR-T cell therapy is a landmark event representing a novel way to harness the immune system to fight cancer. Nephrologists have to work closely with cancer specialists in learning about these novel agents and their kidney-related effects. Early nephrology consultation with intensive management might be required in patients with severe AKI related to cytokine release syndrome. Judicious use of resuscitative crystalloid fluids may stabilize and reverse AKI in patients with mild cases of cytokine release syndrome. Loop diuretics, albumin, and dialysis might be required in patients with severe cases. The use of IL-6 inhibitors is critical in the treatment of cytokine release syndrome–related complications. Increased awareness of cytokine release syndrome associated with CAR-T cell therapy is essential for all practicing nephrologists who take care of patients with cancer.

Disclosures

None.

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Footnotes

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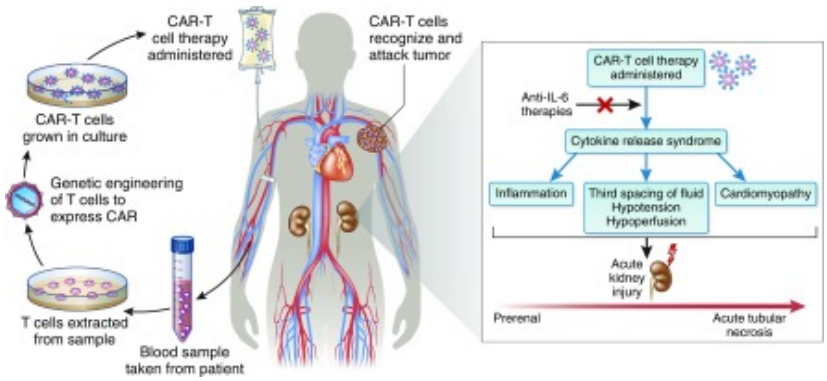
Figures and Tables

Figure 1.



Engineering of Chimeric Antigen Receptor therapy. (Left Panel) T cells are collected *via* apheresis from the patient, a process that withdraws blood from the body and removes one or more blood components (such as plasma, platelets, or white blood cells). The remaining blood is then returned back into the body. T cells are re-engineered in a laboratory. The T cells are sent to a laboratory or a drug manufacturing facility, where they are genetically engineered to produce chimeric antigen receptors (CARs) on their surface. After this re-engineering, the T cells are known as chimeric antigen receptor T (CAR-T) cells. CARs are proteins that allow the T cells to recognize an antigen on targeted tumor cells. The re-engineered CAR-T cells are then multiplied. The number of the patient's genetically modified T cells is "expanded" by growing cells in the laboratory until there are many millions of them. These CAR-T cells are frozen, and when there are enough of them, they are sent to the hospital or center where the patient is being treated. At the hospital or treatment center, the CAR-T cells are then infused into the patient. Many patients are given a brief course of one or more chemotherapy agents before they receive the infusion of CAR-T cells. CAR-T cells that have been returned to the patient's bloodstream multiply in number. (Right panel) Kidney effects of CAR-T cell therapy. CAR-T cell infusion can lead to cytokine release syndrome due predominantly to IL-6 release along with other inflammatory cytokines. AKI results from a combination of hypoperfusion due to third spacing of fluids, hypotension, cytokine-induced cardiomyopathy, and direct inflammatory effects. AKI may be mild and prerenal or severe and due to acute tubular necrosis.

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