CHAPTER 28

Adverse Reactions to Cellular Immunotherapies

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KEY POINTS

1. Cellular immunotherapies offer hope to many patients but have significant adverse event profiles that may or may not be associated with effector function.
2. Oncologic cellular immunotherapies, such as chimeric antigen receptor T-cell therapy, can generate a) on-target, on-tumor; b) on-target, off-tumor; and c) "off-target" adverse effects.
3. The nature and severity of on-target, off-tumor adverse effects in cellular immunotherapy are determined in part by which nontumor tissues express the therapeutic target.
4. Insertional mutagenesis is a notable, although rare, risk of modern, lentiviral-modified cellular immunotherapies.
5. Allogeneic cellular immunotherapies, distinct from autologous therapies, may present the risk of graft-vs-host disease and may have limited efficacy as a result of rejection.
6. Cellular immunotherapies may also be associated with allergic or cryopreservative-associated infusion reactions.

IMMUNE EFFECTOR CELL (IEC) THERAPIES, including chimeric antigen receptor (CAR) T cells, tumor-infiltrating lymphocytes (TILs), and genetically modified hematopoietic stem cells offer new therapeutic options to many patients with otherwise incurable diseases. Following the administration of novel cellular therapies, the long-term persistence of the effector cells raises the possibility of a lifelong cure.[1] The targeted nature of some cellular immunotherapies aims to further improve clinical outcomes by avoiding many adverse reactions associated with nonspecific cytotoxic therapies and cellular therapies. Nonetheless, adverse reactions are still associated with cellular therapies and are often the result of the uncontrolled immune activation that can occur after infusion. Other adverse reactions, both anticipated and unanticipated, must also be considered. Most characterized adverse events are those associated with expected or unexpected expression of the CAR target on nonmalignant cells or tissues. Some adverse events, such as development of secondary malignancies, are exceptionally rare thus far but also not fully character-

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ized. Still other adverse reactions, such as in-vivo replication of the viral vector used to deliver genetic materials, are theoretically possible but have yet to be observed. To better characterize these events, long-term observation is required. Despite the wide array of cellular therapy products targeting a variety of diseases, most seem to share similar adverse reaction profiles. Likewise, management of common clinical outcomes of adverse reactions can be similar despite their association with different cellular therapy agents. Ultimately, scientific and clinical understanding of cellular therapy adverse reactions and their clinical outcomes continues to evolve. As CAR T-cell therapy is most advanced, this chapter focuses primarily on this class of product.

REACTIONS ASSOCIATED WITH EFFECTOR FUNCTION

Targeted cellular immunotherapies are associated with highly potent and specific antitumor responses. For instance, CD19-redirected CAR T cells have generated unprecedented clinical responses in patients with refractory relapsed acute lymphoblastic leukemia (ALL). B-cell maturation antigen (BCMA)-redirected CAR T cells and TILs offer new therapeutic options for patients with multiple myeloma and malignant melanoma/other solid tumors, respectively. Genetically modified hematopoietic stem cells are now a potential curative option for patients with certain hemoglobinopathies, including sickle cell disease. However, adverse reactions associated with these therapies can be severe and even life-threatening.[2]

To broaden use of cellular immunotherapies beyond patients with poor prognoses, adverse reactions must be identified, managed, and ideally prevented. Adverse reactions can be categorized based on presence and severity of symptoms, increasing from grade 1 (mild) to grade 4 (severe), with grade 5 indicating death. Several different grading systems have been developed concurrently to classify adverse reactions to CAR T-cell therapies and help guide interventions.[3] Consensus guidelines have been developed to help standardize adverse event classification, which could be helpful as access to CAR T-cell therapies and other treatments continues to expand.[4] Broadly, reactions associated with cellular immunotherapies can be grouped into three categories: 1) on target, on tumor; 2) on target, off tumor; and 3) "off target."

On Target, on Tumor

A key advantage of targeted cellular immunotherapies is that the cytotoxic response is focused on tumor cells, sparing unintended benign cells and tissues. However, this focused response itself can generate adverse reactions. The therapeutic action of IEC therapy results in immune activation, causing antitumor cytotoxicity. Excessive immune activation and cytotoxicity are associated with cytokine release syndrome (CRS), tumor lysis syndrome (TLS), IEC-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS), and IEC-associated neurotoxicity syndrome (ICANS). Each of these syndromes is distinct and can occur independently, although in practice there is significant overlap in presentation, pathogenesis, and management.

Cytokine Release Syndrome

CRS is characterized by an immune-mediated production of excessive inflammatory markers and cytokines, leading to a positive feedback loop of immune hyperactivation. Signs and symptoms include fever, myalgias, fatigue, headache, tachycardia, hypotension, hypoxia, coagulopathy, and multiorgan failure, and it is potentially fatal (Table 28-1). Clinical manifestations begin typically 2 to 3 days after infusion but may occur as early as hours, and as late as weeks to months, after infusion and may last for days to several weeks.[4,5] Monitoring for CRS is important, as some degree of CRS may occur in many patients treated with CAR T-cell therapy. Laboratory findings show significant elevations in inflammatory cytokines such as interleukin-6 (IL-6), as well as nonspecific markers of inflammation such as C-reactive protein and ferritin. The reported incidence of severe CRS varies but it may occur in up to half of patients treated with CAR T cells.[6] Severe CRS is more common in patients with high pretreatment tumor burden,

TABLE 28-1. Signs and Symptoms of Cytokine Release Syndrome

Constitutional	**Gastrointestinal/Hepatic**
Fever	Nausea
Headache	Vomiting
Fatigue	Diarrhea
Rigors	Transaminitis
Anorexia	Hyperbilirubinemia
Cardiovascular	**Renal**
Edema	Acute kidney injury
Tachycardia	Elevated creatinine and urea
Hypotension	Oliguria
Arrhythmia	**Hematologic**
Acute heart failure	Hypofibrinogenemia
Pulmonary	Cytopenias
Tachypnea	Coagulopathy
Dyspnea	Disseminated intravascular coagulation
Hypoxia	**Musculoskeletal/Integumentary**
Pleural effusion	Rash
Pulmonary edema	Arthralgia
Respiratory failure	Myalgia

after high doses of CAR T cells, after lymphodepleting chemotherapy with fludarabine, and with clinical conditions associated with elevated cytokines before treatment. Several CRS grading systems are in clinical use, each with slightly different criteria for categorizing the degree and management of symptoms shown in Table 28-1. Efforts to develop and implement a single system for characterizing CRS symptoms and severity by clinical guideline development, as well as accrediting body requirements for establishment processes to manage CRS, help standardize provision of care in this context.[4]

The pathogenesis of CRS is a complicated interplay between CAR T cells and host macrophages.[7] Upon activation, CAR T cells directly kill target-positive cells but also secrete several proinflammatory cytokines.[8] Many cytokines are elevated during CRS, including interferon gamma (IFNγ), IL-1, IL-2-receptor alpha, IL-5, IL-6, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), and nitric oxide. In particular,

GM-CSF and CD40L expression on CAR T cells mobilize, activate, and drive proliferation of endogenous macrophages. Myeloid-derived macrophages are likely the major producers of IFNγ, IL-1, and IL-6.[9] Activated macrophages continue to produce macrophage-activating cytokines, driving the positive feedback loop. These cytokines lead to the hyperinflammatory clinical symptoms that typify clinical CRS. Systemic activation of host innate immune cells is a requirement for systemic CRS. Targeted localized malignancies, without a significant disseminated and blood-borne component, may lead to limited or localized CRS compared to CRS in hematologic malignancy.[10]

Management of CRS aims to carefully blunt the inflammatory response while avoiding impairment of antitumor effects. Most patients with B-cell ALL who received CAR T cells and demonstrated partial or complete response experienced at least grade 1 CRS. Corticosteroids can blunt the inflammatory response, but steroids could potentially also suppress CAR T-cell function. Although this has not been definitively shown, the theoretical concern is that reduced CAR T-cell function could put the patient at risk for progressive disease or relapse.

In 2012, tocilizumab, a monoclonal antibody to IL-6, was used for the first time in a CAR T-cell patient to treat fulminant CRS. The patient was treated with CD19-redirected CAR T cells for her refractory relapsed CD19+ B-cell ALL, after which she developed high fever, hypoxia requiring intubation, and hemodynamic instability requiring multiple pressors. Her condition was refractory to steroids and tumor necrosis factor (TNF) inhibitor etanercept. After a cytokine panel showed elevation of IL-6, among others, tocilizumab was administered. Within hours, the patient's conditions stabilized. Importantly, she also remained leukemia free. This case and subsequent clinical experience eventually led to US Food and Drug Administration (FDA) approval of tocilizumab (Actemra; Genentech, Inc) for treatment of severe CAR-T-cell-induced CRS.[11] Preemptive use of tocilizumab in patients with B-cell ALL and high tumor burden appears to reduce the expected risk of CRS without impairing CAR T-cell expansion or persistence.[12] Other agents, such as siltuximab, anakinra, and ruxolitinib, are potential alternatives.[13-15]

Other CAR T-cell approaches that offer promise in mitigating CRS development and severity are under development. For example, the herpes simplex virus type 1 thymidine kinase (HSV-TK) gene, which has been employed as a "suicide gene" for years for earlier generations of T-cell therapies as a safeguard for severe GVHD, is being considered for CAR T cells. CAR T cells cotransduced with HSV-TK can be specifically eliminated upon exposure to ganciclovir, potentially offering in-vivo control; however, such an approach presents its own challenges in that this would essentially eliminate the therapeutic effect of the CAR T-cell therapy and may lead to expression of potentially immunogenic targets.[16] Switchable CAR T cells that fully activate only upon provision of a third-party molecule hold promise, as these cells can be reversibly deactivated in vivo in response to CRS.[17]

Tumor Lysis Syndrome

TLS occurs when a large number of tumor cells are rapidly lysed, releasing potentially toxic intracellular contents and cellular debris, causing downstream organ damage. TLS is not unique to cellular immunotherapies but has been observed with rapid tumor cell destruction after CAR T-cell treatment. CAR T cells are capable of directly lysing tumor cells via perforin/granzyme and Fas/Fas ligand pathways, or indirectly through cytokine production to recruit other antitumor immune cells.[8] As tumor cells are lysed, potassium, phosphorous, lactate dehydrogenase, creatinine, and uric acid levels increase in the peripheral blood. Renal failure, cardiac arrhythmia, neurotoxicity, and vasomotor instability are common clinical manifestations. IECs such as CAR T cells are capable of rapid proliferation and activation after adoptive transfer, and each CAR T cell is capable of killing many tumor cells.[18] Although tumor lysis can exacerbate CRS, TLS is a distinct clinical syndrome. Management of TLS is supportive with fluid resuscitation, monitoring of metabolic parameters, rasburicase, and allopurinol.[19]