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# Medical management of side effects related to CAR T cell therapy in hematologic malignancies

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Chimeric antigen receptor (CAR) T cells are genetically modified T cells, which by design, combine the advantage of human leukocyte antigen (HLA)-independent antigen recognition with the cytotoxic ability of T cells. CAR T-cell technology has evolved considerably with several generations of CAR T cells tested in preclinical studies [1]. CAR T cells targeting CD19 [2–4], LeY antigen [5], and CD22 [NCT02315612] have been used to treat hematological malignancies in humans. Significant distinctions in the CD19-directed CAR T-cell clinical trials from various groups include: scFvs derived from separate hybridomas, inclusion of disparate signaling domains (CD28 or 4-1BB), genetic modification methodology, and dose/preparative regimens prior to CAR T-cell infusion. Despite the differences, early phase I/phase II CAR T-cell trials targeting CD19 have shown comparable and impressive clinical outcomes at multiple institutions. As this immunotherapeutic approach becomes more readily available outside of the clinical trial context, it is paramount for oncologists to be able to recognize and manage the unique side effects associated with CAR T-cell therapy. Some of the common adverse events associated with the use of CD19-targeted CAR T cells include cytokine release syndrome (CRS), macrophage activation syndrome (MAS), neurological side effects, tumor lysis syndrome (TLS), and on-target/off-tumor toxicities. These toxicities have been reported in all CD19-targeted CAR T cell clinical trials independent of CAR design and genetic modification methodology used. Other theoretical (but not reported) side effects with CD19-specific CAR T-cell therapy include insertional mutagenesis and immunogenicity of genetically engineered T cells [6].

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**Declaration of Interests**

RJ Brentjens is a scientific co-founder of, reports receiving a commercial research grant from, has ownership interest (including patents) in, and is a consultant/advisory board member for JUNO Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Activation of CAR T cells after cognate antigen encounter leads to production of supra-physiologic levels of cytokines that trigger a syndrome of temporary and reversible systemic inflammatory state termed ‘cytokine release syndrome’. CRS comprises of clinical and biochemical components. Clinical CRS can include all or some of the following features: fevers, hypotension, hypoxia, capillary leak syndrome, respiratory distress, and/or neurological disturbances [2]. Additionally, biochemical CRS includes elevation of select cytokines, elevations in hepatic enzymes, increased ferritin, increased triglycerides, hypofibrinogenemia. Interferon-gamma (IFN-γ), Interleukin-6 (IL-6), soluble IL-2Rα (sIL-2Rα) and IL-10 among other cytokines are commonly elevated [2,3]. CRS can arise days to weeks after CAR T-cell infusion [2,7,8].

Signs and symptoms of CRS can range from mild to life-threatening. Our group at MSKCC has identified criteria for severe CRS (sCRS), and this includes patients with a triad of persistent fevers (>38°C) for more than 3 days, clinical derangements (including hypotension requiring at least one vasopressor, hypoxia with PO2 < 90% and/or neurologic disturbances) and select cytokine elevations (at least one cytokine with maximum fold change of 250 or two cytokines with maximum fold change of at least 75) [2]. A different grading system has been utilized by other groups which categorizes patients with progressively worsening symptoms and signs into grade 1 through 5 CRS [8]. Severity of CRS has been suggested to be associated with high tumor burden [2,8] and CAR T-cell expansion *in vivo* [7,8]. Patients with severe symptoms/signs of CRS require monitoring in an intensive care setting. Analysis of laboratory data from CD19-directed CAR T-cell therapy at MSKCC by the researchers at the institution demonstrated that daily C-reactive protein (CRP) monitoring can serve as a surrogate biomarker in identification of these high-risk patients [2]. Progressively worsening CRS can lead to multi-organ dysfunction including (but not limited to) cardiovascular, pulmonary and renal failure. Fortunately, with timely and appropriate management, CRS is reversible in the vast majority of patients despite severe grade 3–4 abnormalities.

Patients with CRS need symptomatic and supportive management such as treatment with anti-pyretics and intravenous fluids. We initiate empiric broad-spectrum antibiotic coverage in the setting of fever, as these patients may have a concurrent infection [9]. sCRS or ≥ grade 3 toxicities usually need pharmacologic intervention with corticosteroids and/or anti-cytokine therapy. However, corticosteroid use can be lymphotoxic and can hinder the intended anti-tumor effects of CAR T cells. Patients treated with corticosteroids early on after CAR T-cell therapy may relapse [2] or stay in remission [10], making it currently unclear how outcome is influenced in such a clinical situation. Anti-cytokine therapies may be a superior initial choice, particularly with emerging evidence about IL-6 in the context of severe CRS symptoms [2,8]. Treatment with IL-6 receptor blocking antibody tocilizumab [8] ameliorates CRS and preserves CAR T-cell function as demonstrated by researchers at both MSKCC [2] and at UPenn [3]. Management with corticosteroids may be prudent only for cases of tocilizumab-refractory CRS.

A subset of patients with CRS manifest symptoms similar to macrophage activation syndrome or hemophagocytic lymphohistiocytosis (HLH). Such patients can have liver dysfunction with hepatosplenomegaly, increased ferritin levels and may be coagulopathic

with decreased fibrinogen levels. A combination of these clinical features along with elevations in characteristic cytokines IFN-γ, IL-10 and IL-6 [3,11,12] often indicates MAS or HLH associated with CRS. Although familial or primary HLH is due to genetic aberrations [13] causing defective release of cytolytic granules, secondary HLH (or MAS) can be triggered by immune dysregulation. CRS is one such immune trigger leading to MAS or secondary HLH. However, these patients may or may not have mutations in the HLH-predisposing genes [14]. Intervention for HLH with anti-cytokine therapy or corticosteroids should be balanced with the risks of prematurely abrogating CAR T-cell efficacy by unnecessary administration of immunosuppression. It is prudent to have increased vigilance and pre-emptive clinical and laboratory monitoring as MAS/HLH effects, though temporary, can be severe.

Following CD19-targeted CAR T-cell therapy, patients may also develop neurological side effects such as confusion, delirium, word-finding aphasia, and these can be as severe as coma and/or seizures. Some of these patients may require prophylactic intubation for airway protection. Encephalopathy in children can manifest as increased irritability (younger children) to delirium in adolescents. CAR T cells may or may not be detectable in the cerebrospinal fluid (CSF) of these patients [2,15]. Therefore, these central nervous system (CNS) toxicities are likely secondary to an inflammatory state rather than the direct effect of CAR T cells on neural tissues [2]. Additionally, neurotoxicity has thus-far not been conclusively shown to correlate with CNS disease [2]. Patients with neurological changes often require a thorough diagnostic evaluation [lumbar puncture, imaging and/or an electroencephalogram (EEG)] to rule out other etiologies, despite the low diagnostic yield. Nevertheless, we invariably initiate seizure prophylaxis prior to CD19-targeted CAR T cell infusion. It remains to be seen if these neurological manifestations are unique to CD19-directed CAR T cell therapy.

Tumor lysis syndrome, comprising of metabolic derangements due to sudden and/or massive tumor-cell lysis, may be seen in some patients treated with CD19-targeted CAR T cells, especially in those with chronic lymphocytic leukemia (CLL) [16]. For this reason, patients are placed on intravenous hydration and may also require prophylactic allopurinol prior to the initiation of conditioning chemotherapy. It is important to recognize that TLS may potentiate the risk of acute renal injury in the setting of renal dysfunction due to CRS.

Toxicities secondary to the interaction of CAR T cells with nontumor/normal cells expressing the target antigen are termed ‘on-target/off-tumor’ toxicities. B cell aplasia resulting in hypogammaglobulinemia is one such side effect with CD19-directed CAR T-cell therapy. In the various clinical trials utilizing CD19-targeted CAR T cells, this effect has been observed to last for weeks to months [2–4,16–19] and has been hypothesized to be a surrogate for CAR T cell persistence. Although researchers at UPenn have demonstrated CAR T cell persistence for >1 year in some cases, our group has shown comparable efficacy despite shorter duration of persistence. Hence, the optimal duration of CAR T-cell persistence is still an unknown. Of note, CD19-targeted CAR T-cell therapy is used as a bridge to allogeneic hematopoietic transplant by the researchers at MSKCC and National Cancer Institute (NCI) [2,15]. Hypogammaglobulinemia can be successfully managed with intravenous immunoglobulin (IVIG) replacement therapy to avoid opportunistic infections.

gCommon strategies employed to reduce the side effects associated with CAR T-cell therapy include splitting the total dose of CAR T cells into multiple days, modifying the dose of CAR T cells based on the tumor burden (for patients with morphologic disease, the dose of CAR T cells infused is decreased to lessen the severity of CRS without compromising efficacy [2]), and incorporating conditioning chemotherapy prior to CAR T-cell infusion [17]. Other novel mechanisms to decrease toxicities are under investigation, including designing a CAR with conditional elimination gene as an 'off-switch' for the infused CAR T cells [20]. In summary, CD19 CAR T cells have emerged as a promising new treatment approach for B-cell malignancies, particularly, for a subset of patients with poor outcome. There is rising need for oncologists to be familiar with this therapy and its unique toxicity profile as this immunotherapeutic approach becomes increasingly available.

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