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 hematologic 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].

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, hypo-fibrinogenemia. Interferon-gamma (IFN-γ), Interleukin-6 (IL-6), soluble IL-2Ra (sIL-2Ra) 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, particu-
larly 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 pre-
serves CAR T-cell function as demonstrated by researchers at
both MSKCC [2] and at UPenn [3]. Management with corti-
costeroids 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 lympho-
histiocytosis (HLH). Such patients can have liver dysfunction
with hepatosplenomegaly, increased ferritin levels and may be
coaagulopathic with decreased fibrinogen levels. A combina-
tion of these clinical features along with elevations in charac-
teristic 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 pru-
dent 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, delir-
ium, word-finding aphasia, and these can be as severe as coma
and/or seizures. Some of these patients may require prophylac-
tic intubation for airway protection. Encephalopathy in children
can manifest as increased irritability (younger children) to delir-
ium 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 second-
ary 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 manifesta-
tions are unique to CD19-directed CAR T cell therapy.

Tumor lysis syndrome, comprising of metabolic derange-
ments 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 hydra-
ination 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 persis-
tence. 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 design-
ing 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 immunother-
apeutic approach becomes increasingly available.

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.

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