Cytokine Release Syndrome Biology and Management

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Abstract: The successful application of chimeric antigen receptor (CAR) T cells for the treatment of relapsed and refractory B-cell malignancies has ushered in a new frontier for the immunotherapy of cancer. Despite its successes, CAR T-cell therapy presents several challenges. Cytokine release syndrome (CRS) triggered by robust and exponential CAR T-cell expansion is the most common adverse effect and may be severe or life-threatening. Although modulation of the interleukin 6 axis was appreciated early on as a means to manage CRS, the exact underlying mechanisms leading to severe CRS remain to be elucidated. What is clear is that severe CRS involves recruitment of the broader immune system into a hyperinflammatory and unregulated state. Myeloid-derived cells appear to play a critical role in this regard and are at the center of active investigation. In this article, we will focus on important elements of CRS, the clinical manifestations, underlying biology, and management strategies including grading, supportive care, and treatment via immunosuppression.

Key Words: CAR T cells, cytokine release syndrome, IL-6, macrophage, monocyte, tocilizumab, toxicity

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Successful chimeric antigen receptor (CAR) T-cell therapy in patients with acute lymphoblastic leukemia and non-Hodgkin lymphoma is often associated with severe or life-threatening toxicities. One of the most common toxicities associated with CAR T-cell treatment is cytokine release syndrome (CRS), a potentially severe and life-threatening inflammatory syndrome consisting of and driven by elevations in inflammatory mediators, and which is characterized by fever, hypotension, hypoxia, organ dysfunction, and other significant clinical manifestations to varying degrees.[1–7] Although a high frequency of responding patients (90% or more for currently available commercial products) will develop some degree of CRS following initiation of treatment, this powerful immune activation is tightly coupled to antitumor activity and the impressive response rates that have been observed with CAR T-cell therapy.

While the most notable cause of CRS is the systemic release of inflammatory cytokines from infused CAR T cells and bystander immune cells as a result of target cell recognition and subsequent killing, the precise biological mechanisms responsible remain to be completely defined. The development of CRS and its ensuing severity are now broadly accepted to be related to factors including disease burden, CAR structure and dose, and lymphodepletion conditioning regimens.[8,9] Identification of these risk factors has contributed to improved strategies for CRS management and patient care. Likewise, further elucidation of the underlying biological pathways responsible for the development of CRS will facilitate prevention, identification, and treatment in patients receiving CAR T-cell therapy.

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CLINICAL FEATURES OF CRS

The presentation of CRS in patients receiving CAR T-cell treatment generally begins within 1 week, but can occur as early as 1 day, following infusion with a characteristic fever accompanied by malaise, myalgia, and other flulike symptoms.[6,10,11] However, from that point on, symptoms range widely in scope, severity, and duration between patients. In severe cases, patients may experience hypotension, capillary leak, hypoxia, pulmonary edema, multiorgan failure, and potentially death.[9,12]

Low-grade cases of CRS may be self-limiting with supportive care; however, depending on the severity, patients may require advanced intervention in the form of intensive care and/or immunosuppressive therapy including corticosteroids, tocilizumab (anti–interleukin 6 [IL-6] receptor antagonist), vasopressor support, or mechanical ventilation.[6,11,13] The time to onset, peak, and the duration of CRS are determined by a multitude of factors. For example, CAR therapies containing a CD28 versus 4-1BB costimulatory domain generally lead to faster onset of CRS, by as much as 7 days, compared with the latter.[12,14] Additionally, the magnitude of CAR T-cell activation and expansion has a direct bearing on the development and severity of CRS. Factors such as these and others that contribute to CRS development will be discussed below in additional detail. The duration of CRS is also variable, but typically resolves within a few weeks following CAR T-cell administration.

Chimeric antigen receptor T cells undergo activation and subsequent proliferation following antigen recognition with a resulting exponential expansion in cell numbers. This process occurs rapidly, usually within days, for B-cell antigen–directed CAR T-cell products owing to the plethora of circulating targets in the form of normal B cells and is likely a key factor owing to their clinical success as compared with CARs targeting solid tumors. The same reasoning may also partially explain the widespread incidence and severity of CRS in patients with B-cell malignancies.

Following this interaction, target cells quickly undergo CAR T-cell–mediated cytolysis, with an accompanying release of many inflammatory cytokines and chemokines from activated CAR T cells, bystander immune cells, and bystander nonimmune cells. This widespread immune activation becomes amplified, ultimately leading to the systemic inflammatory state that is defined by CRS. To date, key inflammatory cytokines thought to play central roles during CRS are IL-6, interferon γ (IFN-γ), and IL-1, although a plethora of other cytokines and chemokines are up-regulated as well, including tumor necrosis factor α (TNF-α), IL-2, soluble IL-2Ra, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF), soluble gp130 (sgp130), macrophage inflammatory protein 1α, and monocyte chemoattractant protein 1.[1,5,15]

Initially, a large burst of CAR T-cell–derived IFN-γ and TNF-α stimulates bystander immune cells and endothelial cells, leading to the release of other inflammatory mediators including IL-6

and IL-1 (Fig. 1). Specific cellular sources of the cytokines and chemokines that contribute to this cascade include activated non-CAR T cells and myeloid cells such as monocytes, macrophages, and dendritic cells (DCs). Specifically, peak levels of IFN-γ, IL-6, sgp130, and soluble IL-6R, among others, have been shown to correlate with the development of severe CRS in patients compared with those with lower-grade CRS.[15] Additionally, the inflammatory markers C-reactive protein (CRP) and ferritin are associated with severe CRS.[16]

These findings and others point to the now well-recognized parallels that exist in the cytokine profiles of patients with severe CRS and those with macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH).[15–17] It remains to be determined whether the clinical similarities seen in severe CRS and MAS/HLH are indicative of a common role for macrophage dysfunction in contributing to the overall inflammatory state in these patients. Nonetheless, the role of macrophages and potentially other myeloid subsets as critical regulators in the development and exacerbation of CRS has been garnering much attention.

Endothelial activation is another hallmark feature instigated by the hyperinflammatory state seen in severe CRS (Fig. 1). Several of the key cytokines elevated in high-grade CRS, such

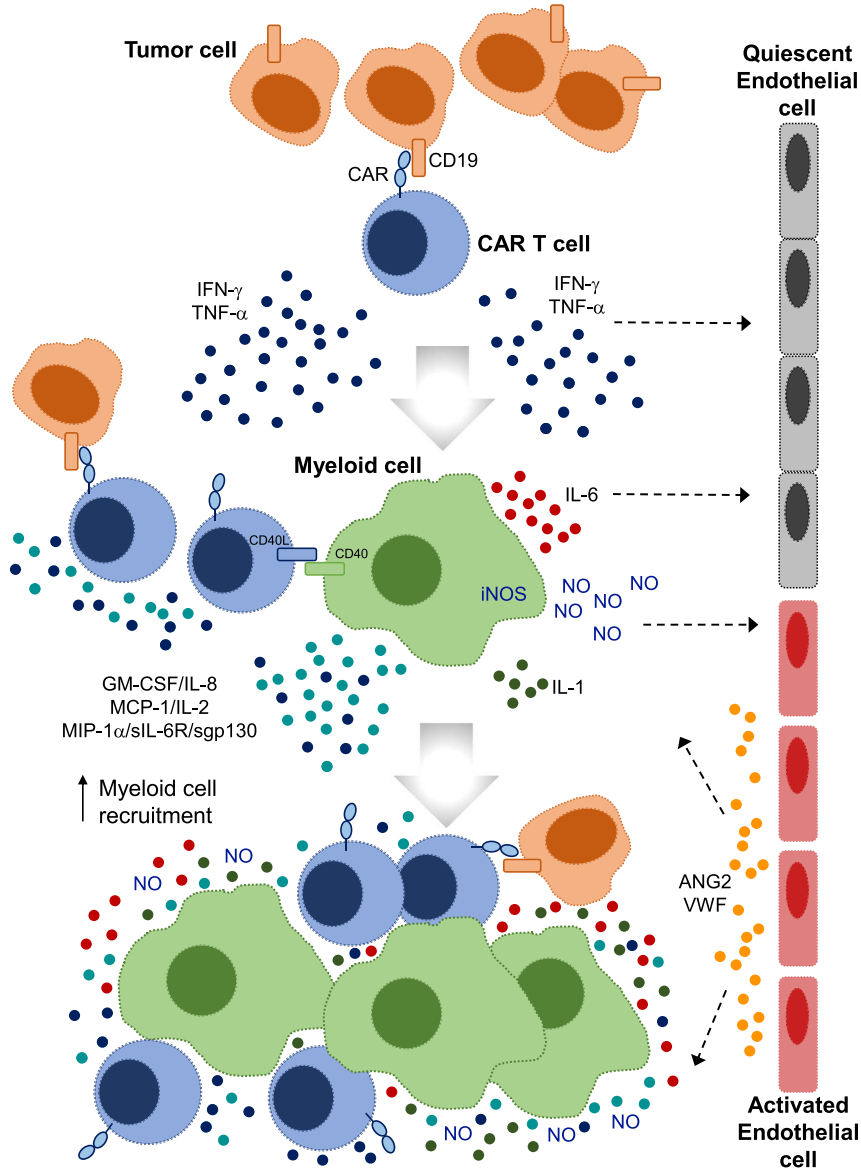

FIGURE 1. Proposed pathophysiology for the development of severe cytokine release syndrome following CAR T-cell therapy. Upon recognition of CD19-expressing leukemia cells via CAR binding, CAR T cells become activated and secrete IFN-γ and TNF-α which stimulates myeloid cell populations including macrophages and DCs, other non-immune cells, and endothelial cells. Activated myeloid cells secrete copious amounts of IL-6, IL-1, and other cytokines and chemokines. Activated endothelium releases stored ANG2 and von Willibrand Factor (VWF). Macrophages also upregulate iNOS leading to abundant production of nitric oxide (NO) which promotes vasodilation and hypotension. Possible cross-talk mechanisms between activated CAR T cells and macrophages/myeloid cells via cell-to-cell interactions (eg: CD40-CD40L) leads to enhanced myeloid activation. Highly-activated CAR T- and myeloid cells further exacerbate the inflammatory condition through robust cytokine/chemokine production which culminates in additional and uncontrolled immune cell recruitment, activation, and cytokine release.

as IFN-γ, IL-6, monocyte chemoattractant protein 1, and IL-8, have the capacity to induce endothelial cell activation. Activated endothelium then releases angiopoietin-2 (ANG2) and von Willebrand factor (VWF), both of which are elevated in CRS patients and are associated with severe CRS.[5,18,19] Angiopoietin-2 release leads to increased endothelial permeability and further activation of the endothelium.[20] Elevated serum levels of ANG2 and VWF are thought to potentially lead to hemodynamic instability, capillary leak, and coagulopathy that is observed in patients with severe CRS.

PRECLINICAL MODELS OF CRS

Historically, there has been an absence of adequate preclinical modeling of CRS in vitro or in laboratory animals, which prevented clinicians and researchers from predicting the development of CAR T-cell–induced CRS, studying its underlying biology and evaluating clinical intervention strategies. Fortunately, with the recent advancement of 2 xenogeneic mouse models of CRS, progress has been made in better understanding the biological factors involved. In 1 model, severe CRS was induced in SCID-beige mice within days of CD19 CAR T-cell injection and was characterized by a systemic inflammatory response with a cytokine profile that highly resembled CRS reported in human studies, including IL-6 (murine-derived) and IFN-γ (human-derived).[21] Additionally, several inflammatory cytokines were highly correlated with CRS severity and survival. Importantly, intervention with IL-6 receptor blockade protected mice from severe CRS, as did treatment with anakinra, an IL-1 receptor antagonist. Myeloid cells, particularly macrophages, were demonstrated to be potent drivers of IL-6 production and exhibited elevated inducible nitric oxide synthase (iNOS) expression. Increased iNOS production leads to elevated nitric oxide, which stimulates vasodilation and hypotension, both of which occur during severe CRS.

In the second model, a humanized mouse was established using triple-transgenic NSG mice expressing human stem cell factor, granulocyte/macrophage-CSF, and IL-3, and recapitulated important features of severe CRS including fever and a systemic inflammatory cytokine response after CD19 CAR T-cell treatment.[22] Human monocytes were found to be the key producers of IL-6 and IL-1 and were required for the development of CRS. Together, these unique murine models closely mimic many key characteristics of human CRS induced by CAR T cells and provide critical insights into the mechanisms driving CRS. Last, these models, and any future derivations in development, will make it possible to further investigate the pathophysiology and provide preclinical avenues for evaluating the efficacy of immunosuppressive strategies to mitigate CRS.

ROLE OF MYELOID CELLS IN CRS

The cellular landscape of CRS is undoubtedly complex, and many questions remain unanswered regarding the specific cell types and the extent of their contribution to the onset and exacerbation of CRS. Although several cytokines, namely, IL-6, IL-1, and IFN-γ, have emerged as core players, there may be other inflammatory mediators and/or signaling pathways that have key roles in severe CRS. Identifying the cellular sources of these cytokines is equally important. To this point, much evidence gathered from clinical studies and observations made in animal models points to a critical role for myeloid-derived monocytes and macrophages and their inflammatory products.

Myeloid cells appear to exert their influence in CRS through the release of inflammatory cytokines. In the SCID-beige mouse model of CRS,[21] myeloid cell populations exhibited both quantitative and qualitative changes brought on by CAR T-cell administration. Increased numbers of DCs, macrophages, and monocytes were found at sites of tumor-CAR T-cell interaction. Although DCs showed up-regulated IL-6, macrophages and monocytes exhibited increased expression of IL-6, granulocyte colony stimulating factor, macrophage colony stimulating factor, and IL-12. Macrophages were the major producers of iNOS, with monocytes and DCs contributing to a lesser degree. In the humanized mouse model,[22] CRS was mediated primarily by monocytes as determined by monocyte-specific ablation, which prevented the development of CRS in mice receiving CD19 CAR T cells. Single-cell gene expression analysis of the major myeloid cell populations showed that monocytes expressed high levels of IL-1, IL-6, IL-8, CCL2, CCL8, and CXCL10. Taken together, these 2 models directly implicate monocytes and macrophages as important drivers of CRS.

Although these studies have shed light on the involvement of these cell types, much remains to be explored in regard to additional factors and precise mechanisms that contribute to myeloid cell recruitment and activation following CAR T-cell administration. For example, direct cell-to-cell interactions between activated CAR T cells and myeloid cells within tumor sites, particularly the nature of these interactions, are likely to affect the ensuing immune cascade. The importance of this scenario was demonstrated when enforced CD40-CD40L interactions between CAR T cells and myeloid cells increased the severity of CRS in mice.[21] Additional mechanisms that contribute to myeloid cell activation following CAR T-cell infusion are still under investigation. Therefore, strategies aimed at modulating these myeloid-derived cells should be investigated as another possible avenue for mitigating toxicity. In the meantime, there are several approaches available to minimize the risk for and manage CRS and severe CRS.

OPTIMAL TOXICITY MANAGEMENT BEGINS WITH PATIENT AND PRODUCT SELECTION

Every individual, engineered cellular therapy product, even those using the same CAR construct, has a unique capacity for antitumor efficacy, as well as propensity to induce toxicity owing to patient-specific immunologic factors. These include, but are not limited to, lifetime exposure to cytotoxic agents given over the course of therapy, type and timing of exposure to the most recent cytotoxic agent prior to apheresis, history of hematopoietic stem cell transplantation (HSCT) and timing from HSCT, patient age as a surrogate for T-cell (and other immune cell) telomere length and capacity to respond and/or persist once activated, the type of malignancy, degree of tumor burden and its pace of expansion, and patient comorbidities and advanced age that may limit tolerability of CRS and other toxicities.

Similarly, different CAR T-cell products behave differently and have slightly different toxicity profiles.[1–3,10,23–30] Therefore, the most important step in managing CRS in patients receiving CAR T-cell therapy is to administer them to only those patients who are likely, with excellent supportive care and timely intervention, to tolerate CRS after product-specific factors have been considered. Similar to current practice prior to HSCT, potential CAR T-cell recipients should be reviewed by the institution's cell therapy or HSCT committee and determined to be fit and appropriate for therapy before proceeding. Practitioners should also decide ahead of time whether earlier and/or more aggressive intervention for toxicity is warranted for a particular patient.

DELAY CAR T-CELL INFUSION FOR NEW OR UNCONTROLLED INFECTIONS, INCLUDING SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Infectious complications of prior therapies are common, particularly in highly pretreated patients or those relapsing after HSCT.

These are likely to exacerbate CAR T-cell toxicities if they are new or uncontrolled at the time of infusion, and lymphodepletion regimens will interfere with the patient's ability to immunologically control infection. To minimize complications, cell infusion should be delayed in all patients with a new or uncontrolled suspected or proven infection. New-onset fever alone is sufficient to trigger a delay until appropriate evaluations for infection are resulted, and patients are afebrile for at least 48 hours.

Bacteremia should be managed with appropriate antibiotics with negative blood cultures without fever for at least 48 hours prior to infusion.[31] New fungal disease should be managed with appropriate antimicrobials, and CAR T-cell infusion withheld until the infection is controlled. Although most practitioners agree that fungal disease does not need to be eradicated prior to infusion as this often takes weeks to months for complete resolution, proximity of lymphodepletion with fludarabine and cyclophosphamide to the diagnosis of fungal infection may place the patient at higher risk of a poor outcome.[31]

Viral infections pose a different challenge. Early case reports suggested that concomitant infection with a respiratory virus was a contributing factor in the death of a patient receiving CD19 CAR T cells.[32] Indeed, it is prudent to delay CAR T-cell infusion when a new viral infection is suspected or confirmed. If the infection is causing minimal symptoms, CAR T-cell infusion may proceed in cases where delaying it would likely lead to a poor clinical outcome, such as with a rapidly progressive malignancy; understanding this may require modulation of the supportive care and anticytokine therapy intervention plan.

In the case of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), however, CAR T-cell infusion should be delayed until the infection is no longer considered to be transmissible if at all possible. Many, but not all, SARS-CoV-2 patients develop a hyperinflammatory state, sometimes beginning after initial improvement, which can be even more severe than the initial infection.[33] This state is often characterized by new-onset lymphopenia and elevated inflammatory markers, CRP, erythrocyte sedimentation rate (ESR), and ferritin. Therefore, although it is acceptable to proceed with CAR T-cell infusion in patients with rapidly progressive disease who have recovered from the initial effects (including fever) of SARS-CoV-2,[31] careful evaluation for SARS-CoV-2–related hyperinflammatory state should be performed just prior to lymphodepletion, and lymphodepletion and CAR therapy should be delayed if this is suspected. Other practical factors should also be considered before proceeding, such as the availability of personal protective equipment, isolation bed space, and policies at each institution.

SIMPLIFIED CONSENSUS CRS GRADING

Early CAR T-cell investigators quickly found that the available definition and grading schemes for CRS (CTCAEv4)[34] were inadequate. While many groups proposed differing grading criteria, most clinical trials registered with the US Food and Drug Administration to date have used the 2014 Lee criteria.[6] This multi-institutional group based grading on the interventions required to stabilize hypotension and/or hypoxia due to CRS or the grade of end organ system involvement, if present. They also tied grading to a management algorithm that took patient comorbidities into consideration. Subsequent grading systems including CARTOX and the CTCAE v5 either adopted the Lee criteria outright or modified it slightly.[14,35]

As CAR T-cell therapies became more widely used and as multiple grading schemes were being used, the community needed an international consensus grading system that is easy to utilize at the bedside. The American Society for Transplantation and Cellular Therapy (ASTCT) published consensus CRS and immune effector cell–associated neurotoxicity syndrome (ICANS) grading recommendations in 2019 to serve this need.[36] In regard to CRS, fever defined as a temperature ≥38°C must be present at the onset in order for CRS to be diagnosed, and the grading was simplified from the 2014 Lee criteria by removing the contribution by end-organ dysfunction except for hypotension and hypoxia, which are now graded using simple, easily identifiable-at-the-bedside criteria (Table 1). Most investigators, practitioners, and regulatory agencies now strongly recommend the use of the ASTCT criteria for all CAR T-cell products, both commercial and investigational.

BASELINE EVALUATIONS FOR OPTIMAL CRS MANAGEMENT

In addition to fever, hypotension, and hypoxia from capillary leak, CRS may involve other systems, and their assessment and optimization prior to infusion are critical. Electrolytes are often deranged during CRS. Tumor lysis syndrome may develop or, conversely, profound hypokalemia and hypophosphatemia. The latter is common during the CAR T-cell exponential expansion phase as replicating cells incorporate these critical intracellular elements quickly outstripping the circulating supply. Normalization of electrolytes prior to cell infusion is essential.

Signs, symptoms, and laboratory derangements seen particularly in cases of severe CRS often overlap with MAS/HLH. Notably, ferritin often becomes extraordinarily elevated when MAS/HLH occurs. It remains to be determined whether MAS/HLH is a natural progression of CRS or whether they are similar but have distinct pathologic mechanisms. Regardless, screening for a preexisting inflammatory state with CRP, ESR, and ferritin will aid in interpreting repetitive measurements of these after CRS develops. Although a malignancy itself can lead to derangements in these markers, unexplained elevations at baseline should prompt the practitioner to consider a new infection that may need to be addressed.

Marked hypofibrinogenemia and coagulopathy frequently develop in patients with CRS but may also present even after the acute signs of CRS have resolved. Establishing and correcting baseline fibrinogen or coagulation factors is therefore important to minimize complications after cell infusion.

Finally, cardiac toxicities are more recently being appreciated particularly in the elderly. These may range from prolonged and persistent sinus tachycardia, arrhythmias, prolonged QTc, diminished left ventricular ejection fraction (LVEF) or ventricular strain, heart failure, and myocardial infarctions.[31,37] Although arrhythmias are less common in pediatrics,[38,39] diminished LVEF occurs not infrequently in both adults and children. Even in patients with normal baseline LVEF, baseline global longitudinal ventricular strain may be deranged, particularly in those with prior anthracycline exposure, and may identify those at higher risk of left ventricular dysfunction during CRS.[38] Further, significant cardiac events tend to correlate with elevations in troponin and/or pro–brain natriuretic peptide (pro-BNP).[31,37,38] Baseline echocardiogram, including assessment of global longitudinal ventricular strain when possible, and 12-lead electrocardiogram together with measurement of troponin and pro-BNP should be obtained prior to CAR T-cell infusion.

Additional evaluations aimed at minimizing ICANS should be performed; however, a discussion of these is outside the scope of this article.

EARLY AND HIGH-QUALITY SUPPORTIVE CARE IS THE CORNERSTONE FOR EFFECTIVE CRS MANAGEMENT

Sinus tachycardia and fever are commonly the first symptoms of CRS to develop. Patients who are infused with cells in

TABLE 1. ASTCT CRS Consensus Grading[36]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With:				
Hypotension	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by‡	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.

*Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having grade 3 CRS.

‡Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

the outpatient environment should have a caregiver with them 24 hours a day and be instructed to seek emergent medical care should fever (temperature ≥38°C) develop. All patients should be evaluated by a medical professional trained in the management of CAR T-cell toxicities without delay and admitted to the hospital if not already. At a minimum, blood cultures and broad-spectrum antibiotics should be implemented. Electrolyte derangements, cytopenias, or coagulopathies should be managed appropriately. Frequent vital signs should be performed looking in particular for evidence of early hypotension, peripheral vasodilatation, widened pulse pressure, and/or hypoxia or other signs of capillary leak.

Hypotension and aberrations in perfusion should be managed aggressively with an intravenous fluid (IVF) bolus but should be repeated no more than once before transitioning to a vasopressor.[31] Experience has demonstrated that sole reliance on IVFs in the setting of ongoing hypotension with or without capillary leak and peripheral vasodilatation will only contribute to worsening toxicity, including the more rapid development or worsening of hypoxia, given the extremely short benefit from crystalloids as capillary leak develops. Rather, early transition to vasopressors will better preserve organ perfusion while not exacerbating capillary leak.

During CRS, profound hypokalemia, hypophosphatemia, and other electrolyte derangements may develop.[2,40] Aggressive repletion may be necessary, often several times a day particularly for hypophosphatemia. Such supplementation will involve large volumes of IVF, making it even more important to move from IVF boluses to vasopressors for the management of hypotension early in the course.

Given the risk of cardiac events, particularly in older patients, and diminished LVEF, even in younger patients, electrocardiogram, ECHO, troponin, and pro-BNP should be performed on all patients requiring vasopressors and repeated periodically until CRS has resolved.[31,37,38] Derangements in any of these tests from baseline should prompt additional interventions as appropriate with guidance from the cardiologist.

Coagulopathy and profound hypofibrinogenemia are common during and after moderate to severe CRS. These laboratory tests should be followed closely during CRS, increasing in frequency as severity of CRS increases. A normal or elevated fibrinogen, particularly when measured early in the CRS course, should not be reassuring as it is an acute phase reactant and is often initially elevated. Although exact mechanisms are not known, ongoing consumption of fibrinogen and other coagulation factors at a rapid pace along with evidence of endothelial disruption (ANG2 and VWF) may result in subsequent bleeding and is associated with severe CRS and ICANS.[5,31] Therefore, aggressive transfusions with cryoprecipitate or fresh frozen plasma are critical, along with maintaining adequate platelet counts, in preventing potentially catastrophic events.

Profound hypofibrinogenemia along with a dramatic and rapid rise in ferritin in the right clinical context may be a harbinger for MAS/HLH. At a minimum, ferritin along with ESR and/or CRP should be trended daily during the CRS period. Ferritin values exceeding 100,000 ng/mL are not uncommon as MAS/HLH develops. Significant elevations in ferritin should prompt a standard workup, including measuring triglycerides, fibrinogen, and CD25 (sIL2ra). Patients with CAR T-cell–related MAS/HLH may not have significant lymphadenopathy or splenomegaly often seen in secondary MAS/HLH or may have had these at baseline owing to malignant infiltration of these organs, making diagnosis further problematic. Finally, obtaining a bone marrow biopsy to assess for hemophagocytosis is often not feasible in these critically ill patients, and the absence of it does not rule out MAS/HLH. Therefore, the diagnosis of CAR T-cell–related MAS/HLH is a clinical one supported by laboratory data.

Other toxicities have been associated with CAR T-cell therapy and CRS. A comprehensive review of all of these is outside the scope of this article but is addressed in more detail in the recently published Society for Immunotherapy of Cancer's clinical practice guideline on immune effector cell–related toxicities.[31]

ANTICYTOKINE THERAPY FOR CRS SHOULD BE TIMELY AND COMMENSURATE WITH RISK

Despite high-quality supportive care, many CAR T-cell patients may not tolerate moderate or severe CRS or even prolonged mild CRS. Midgrade fever and sinus tachycardia lasting longer than 24 hours may be intolerable to elderly patients and those with

comorbidities. In comparison, this and even more advanced CRS is easily tolerated by most children and younger adults.[2,6,30] Very early onset of CRS (within 24 hours) and products containing a CD28 costimulatory domain tend to correlate with increased risk of developing severe or life-threatening CRS.[31] Therefore, the timing of anticytokine intervention in patients should take these factors into consideration.

Although more formal studies are needed, it is generally accepted that early use of tocilizumab, an anti–IL-6 receptor monoclonal antibody, which is the only US Food and Drug Administration–approved therapy for CRS, or corticosteroids does not affect efficacy or the long-term duration of response in B-cell malignancies.[41] Whether this holds true for the prophylactic use of these agents before CRS begins remains a question under study.

Most experts agree that any patient who requires a vasopressor to manage hypotension should also receive tocilizumab without delay.[31] Multiple doses of tocilizumab may be needed for adequate control of CRS. While many algorithms have been proposed, it is generally accepted that second and greater doses of tocilizumab should be accompanied by corticosteroids.[31] Third-line agents, such as anakinra (IL-1 receptor antagonist) and siltuximab (anti–IL-6 antibody), should be strongly considered if CRS progresses despite more than 2 doses of tocilizumab and steroids. How rapidly one moves through this generalized algorithm depends on the timing of CRS onset and the individual product and patient-specific risk factors.

If MAS/HLH is suspected, even if in the early stages, prompt intervention with tocilizumab is warranted as this agent can reverse early CAR T-cell–associated MAS/HLH. Persistent fever with profound hypofibrinogenemia and/or profoundly elevated ferritin may be sufficient to trigger intervention with tocilizumab. In general, the earlier tocilizumab is utilized, the better the outcome.[31] Late or severe MAS/HLH is often not responsive to tocilizumab, perhaps owing to more widespread and self-propagating (i.e., no longer dependent on the IL-6 axis) immunologic hyperactivation. While multiple doses of tocilizumab may be needed, as with CRS corticosteroids should be administered no later than with the second dose of tocilizumab, and alternative agents should be considered if 3 or more doses of tocilizumab are needed. The role for etoposide, a standard treatment for non–CAR T-cell–associated MAS/HLH, has not been determined in CAR T-cell–associated MAS/HLH but remains a therapeutic option in cases refractory to tocilizumab.[31]

MANAGEMENT OF CRS WILL EVOLVE

The underlying biology of CAR T-cell–induced CRS is exceptionally complex. Yet, since the successful arrival of CAR T-cell therapy to the clinic and the subsequent approval of 4 commercial products, significant progress has been realized leading to the identification of many factors involved in CRS. Some of the inflammatory mediators involved may represent potentially actionable targets for therapeutic intervention during severe disease, as IL-6 has been via administration of tocilizumab.

As additional insights into the mechanisms of CRS formation and propagation are elucidated, as CAR T-cell therapy extends to other types of cancers, and as additional non–T-cell–based engineered cell therapies are developed, such as natural killer cells transduced with CARs, it will be necessary to expand our knowledge of the associated toxicities such as CRS given that the underlying biological mechanisms leading to toxicities may differ. These management recommendations will then likely need to be modified. Ongoing clinical trials studying the efficacy of anakinra to manage or prevent CRS and ICANS are ongoing, and these results, too, may alter the CRS treatment paradigm. Even in light of this, additional drugs or methods for managing or preventing CRS are in need of development and formal study.

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