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REVIEW

Cytokine Release Syndrome: Current Perspectives

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Abstract: Chimeric antigen receptor T cell (CART) therapy represents a novel and a paradigm-shifting approach to treating cancer. Recent clinical successes have widened the applicability of CD19 CART cells for the treatment of relapsed/refractory B-cell NHL, namely tisagenlecluce and axicabtagene ciloleucel. Tisagenlecluce is also approved for relapsed and/or refractory B-ALL up to age 25. CART therapy is associated with unique and potentially life-threatening toxicities, notably cytokine release syndrome (CRS). A better understanding of the pathogenesis of CRS is crucial to ensure proper management. In this review, CRS definitions, profiles, risk factors and grading systems are discussed. Finally, current and novel investigational approaches and therapies for CRS are summarized.

Keywords: cytokine release syndrome, chimeric antigen receptor T-cell therapy

Introduction

Chimeric antigen receptor (CAR)-T (CART) cell therapy represents a novel and a paradigm shifting approach to treating cancer. Using genetically modified cytotoxic immune T cells to target tumor-specific antigens, this immunotherapy platform has resulted in durable remissions in relapsed and/or refractory B-cell non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia (ALL)[1–3] and is showing promising early results in multiple myeloma.[4] Currently, there are two FDA-approved products for the treatment of relapsed/refractory B-cell NHL, namely tisagenlecluce and axicabtagene ciloleucel. Tisagenlecluce is also approved for relapsed and/or refractory pediatric B-ALL up to the age of 25 years.

Structurally, a CART consists of three essential components: an ectodomain, consisting of an extracellular, antibody-derived antigen recognition domain, typically a single-chain fragment variable (scFv) originating from a monoclonal antibody specific for the selected tumor antigen; an endodomain which contains an intracellular T cell receptor (TCR) derived, activating domains from CD3ζ or CD3γ.[5] Additionally, second and subsequent generation CARTs also contain costimulatory domains such as CD28 and 4-1BB. These costimulatory domains are necessary for T cell activation, resulting in significant expansion, proliferation and persistence of the CART cells;[5] Lastly, a transmembrane domain which connects the ectodomain to the endodomain.

Recent clinical successes have helped to thrust CART cells towards wider applicability, including clinical trials for other hematologic malignancies and even solid tumors. Moreover, there is an expectation to expand use of CART beyond specialized academic centers into the wider community practice at large. Use of

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CART cells has brought a unique set of toxicities such as cytokine release syndrome (CRS) and neurotoxicity. Here, we provide an extensive overview of CRS, including risk factors, emerging grading models, and current and emerging strategies for prevention and treatment of CRS.

Defining CRS

CRS represents a potentially serious complication of CART therapy. It is a cytokine-mediated systemic inflammatory response which occurs in concert with in vivo CART activation and expansion.[6] The exact mechanism of CRS remains to be better understood. Cytokines are released when interaction between tumor and immune effector cell occurs; and it can originate not only from the CART cell but also from host immune cells such as macrophages, which respond in part to CART activation.[7]

Clinically, the CRS can present with fevers, myalgias, hypotension and hypoxia. They can be mild and self-limiting, or progress in severity to high-grade fevers, hemodynamic compromise requiring vasopressor support, capillary leak, and severe hypoxia requiring ventilator support. Moreover, clinical manifestations of CRS can also manifest as arrhythmias, renal failure, pleural effusions, transaminitis, coagulopathy, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS),[8] though these typically are uncommon in the absence of hypotension, hypoxia or both.[9,10] CRS can present either by itself or concurrently with immune effector cell-associated neurotoxicity syndrome (ICANS). CRS can vary in time of onset between 1 and 58 days post-CART infusion with median time of onset following CART infusion of 2–3 days.[11–13] The duration of CRS can vary according to the CART construct, manufacturing or therapeutic interventions but typically resolution of CRS is seen within 2–3 weeks of CART infusion.

Cytokines Profile Of CRS

As the name implies, a number of cytokines released during CRS are found to be elevated. The main cytokines implicated in the pathogenesis of CRS include interleukin-6 (IL-6), interleukin-10 (IL-10), interferon (IFN)-γ, monocyte chemoattractant protein 1 (MCP-1) and granulocyte-macrophage colony-stimulating factor (GM-CSF); other cytokines, including tumor necrosis factor (TNF), IL-1, IL-2, IL-2–receptor-α, and IL-8 have also been reported during CRS.[14,15]

IL-6, likely arising from activation of endothelial cells, can cause capillary leakage, hypotension, activation of complement pathway and coagulation cascades, and myocardial dysfunction.[16,17] IFN-γ can cause flu-like symptoms and can also trigger macrophage activation, leading to secretion of host cytokines such as IL-6, TNF-α, and IL-10[15,18] which could further exacerbate CRS. Other biomarkers of endothelial cell activation, such as Angiopoietin-2 and von Willebrand factor, have also been described to predict CRS severity, before CART infusion and during CRS.[19] Non-specific markers of inflammation including ferritin and C-reactive protein (CRP) are also elevated in patients with CRS.[6,20,21] In more severe CRS, particularly those who develop HLH/MAS, additional cytokines such as IL-18, IL8, IP10, MCP1, MIG, and MIP1β have been reported to be elevated and appear to portend a poorer outcome.[6]

Risk Factors For CRS

With increasing utilization of CART and with a better understanding of CRS, there is an unmet need to identify clinical and biochemical factors to better predict CRS, particularly severe CRS cases. It is anticipated that any risk factor which portends in vivo CART expansion and activation would be predictive CRS severity.

Clinical factors include disease burden and marrow involvement, lymphodepletion with fludarabine/cyclophosphamide conditioning, and higher CART infusion doses.[4,19,22,23] Other patient-specific factors such as pre-existent state of inflammation (baseline serum ferritin) and baseline endothelial activation (thrombocytopenia) appear to be predictive of higher grade CRS[2,4,19,24,25] (Table 1).

Efforts are underway to develop and standardize cytokine activation profiles which correlate with CRS severity, to help abrogate it at an earlier stage.[6,24] The group at Memorial Sloan Kettering Cancer Center (MSKCC) showed a 75-fold increase in a panel of seven cytokines (IL-6, IL-5, IL-10, GM-CSF, IFN-γ, fractalkine, FLT-3L)

Table 1 Risk Factors For Development Of Severe CRS

Risk Factors For Severe CRS
Early onset of CRS (within 72 hrs)
High disease burden
Lymphodepletion with flurarabine-based conditioning
High infused CAR-T cell dose
Severe thrombocytopenia
CART cells without selection of $CD8^+$ central memory T cells
High baseline serum ferritin (>1500 μg/L)

from baseline in those with severe CRS.[24] The group at University of Pennsylvania (UPenn) identified an increase in 24 cytokines (including IFNγ, IL6, IL8, sIL2Rα, sgp130, sIL6R, MCP1, MIP1α, MIP1β, and GM-CSF) in the first month after CART infusion to be highly associated with severe CRS.[6] The two groups, however, found differing results predicting severe CRS with CRP peak elevations. The MSKCC group found significant elevations of CRP predictive of severe CRS, while the UPenn group did not find it correlating with severe CRS development although CRP elevation was noted in CRS development,[6,24,26,27] One noteworthy limitation of a cytokine-defined intervention for CRS is the laboratory capabilities and turn-around time for results required for immediate action, particularly in potentially severe CRS. At this time, it is recommended to treat CRS based on clinical symptoms.[10]

Grading Models Of CRS

With widespread availability and use of T-cell directed therapies under clinical trials and as a standard of care, there has been several attempts to establish a consistent and accurate grading system for clinical management and also for trial reporting purposes. CRS is not a new concept. It has been described in the early 1990s. To our knowledge, the first case of CRS was described as a result of systemic inflammation caused by an anti CD3 monoclonal antibody used for organ transplantation.[28] Several monoclonal antibodies (moAbs) have been associated with development of CRS.[29] The prevailing assumption was that CRS could occur within minutes or few hours of moAb infusion, which is clinically different from cell therapies. Thus, the initial grading system proposed using the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v.4.03) was perhaps not optimal for grading of CART-related CRS.

In the earlier phases of CART cell development, there were several grading systems that were used including NCI Consensus Grading,[30] the UPenn grading,[31] and the MSKCC criteria[25] as described previously.

An initial effort focused on enhancing the CTCAE v4.03 CRS[30] to determine categories of mild, moderate, severe and life-threatening CRS. Under this system, grade 1 CRS consisted of presence of fever with or without constitutional symptoms but without organ dysfunction; grade 2 CRS entailed hypoxia (requiring up to 40% FiO2 supplementation), hypotension (responsive to intravenous fluids (IVF) or low-dose vasopressors) and up to grade 2 organ toxicity; for patients to develop grade 3 CRS, they should show higher oxygen requirements (FiO2>40%), use of higher doses of vasopressors (or multiple vasopressors), grade 3 organ toxicity (grade 4 transaminitis); and grade 4 CRS entailed life-threatening symptoms, requirement of ventilator support or grade 4 organ toxicity (except for transaminitis).

The MSKCC criteria[25] had some differences from Lee's criteria. For instance, while the definition of grade 2 or 3 CRS required the need for vasopressors as criteria (similar to Lee's criteria), it was based on the duration of vasopressor use (<24 versus >24 hrs). Patients requiring higher doses of vasopressors for more than 3 hrs were considered as having grade 4 CRS.

In contrast, in the UPenn CRS grading,[31] the definition of CRS grade 2 was less clear requiring "some signs of organ dysfunction" and intravenous fluids were permitted for management except when hypotension was present. If fluids or any dose of vasopressors (for any duration) were required for management of hypotension, then patients were classified as having grade 3 CRS.

These diverse grading systems led to differences in the reported incidence and even severity of CRS in clinical trials. To underscore this issue, for example, a patient with fevers and hypotension responsive to fluids and hypoxia requiring less than 40% FiO2 is classified as having grade 2 CRS (non-severe) per Lee criteria.[10] However, by UPenn criteria, this CRS would be considered grade 3.

This difference was clearly emphasized after an analysis of the JULIET trial of tisagenlecleucel for DLBCL, where experts in the field "re-graded" patients with CRS using the Lee's criteria and compared to UPenn criteria.[30,31] In 31% of cases, the Lee's grading yielded a lower score than the UPenn grading, in 61% it resulted in the same grading and in 8% of cases the Lee grading was higher than that of UPenn.[32]

Another grading model known as the CARTOX system is based on a three-step-based approach that consists of grading, assessment and treatment. The grading of CRS was mainly based on the Lee's criteria using four parameters, namely temperature, presence of hypotension, oxygen requirements and organ toxicity. It specifically defined fever as a temperature >38°C and hypotension as a systolic pressure of less than 90 mmHg. The CARTOX grading also proposed that CRS represents a dynamic process and, accordingly, it required evaluation at least twice a day but more often if there was a justifying change in the clinical condition of the CART recipient.[33]

Most recently, The American Society for Transplantation and Cellular Therapy (ASTCT) developed consensus guidelines for grading CART toxicities including CRS; the authors also summarized previously described grading models.[10] In this new grading system fever, hypotension and hypoxia remained the cardinal features of CRS. While fever was required for the diagnosis of CRS, it did not have to persist during the periods of CRS toxicity. One of the main goals of the ASTCT CRS grading system was to both harmonize and simplify the current grading of CRS in order to facilitate the reporting of cell therapy-related toxicities.

One of the most relevant changes in the ASTCT grading model was the removal of organ toxicity from the CRS grading as these changes occur concomitantly with hypotension and hypoxia and would not likely influence the decision to prescribe anti-IL6 based therapy. A patient with fevers only was considered a grade 1 CRS. Grade 2 CRS required the presence of fevers along with hypotension (without the use of vasopressors) and/or hypoxia requiring low flow oxygen. Grade 3 entailed the presence of hypotension requiring one vasopressor with/without vasopressin and/or hypoxia requiring high flow oxygen. Grade 4 CRS represented a life-threatening condition requiring multiple vasopressors (excluding vasopressin) and hypoxia requiring positive pressure ventilation systems (BIPAP, CPAP or mechanical ventilation); we refer the readers to the ASTCT consensus guidelines which also provides a summary and a side-by-side comparison of all CRS grading models.[10]

Table 2 summarizes the major studies and the grading criteria used.

CRS Treatment And Prevention

CRS generally occurs within days after CART cell infusion. While identification of factors predictive of severe CRS continues to evolve, one mainstay of CRS treatment is to deploy anti-cytokine therapy early in the CRS course to prevent progression into severe life-threatening higher grade CRS.

As many symptoms of CRS can mimic other medical conditions such as sepsis, infection, or adrenal insufficiency, it is of utmost importance that a thorough workup is performed to rule them out. One major challenge remains to identify agents effective for CRS treatment that do not interfere with the cytokine-mediated anti-tumor effects of CART cells.

Tocilizumab

Tocilizumab is humanized IL-6 receptor antagonist moAb which functions by inhibiting both classic and trans-IL-6 signaling on immune effector cells.[34] It works on both membrane-bound IL-6 receptor and soluble IL-6 receptor by competitively competing with IL-6 for binding to both receptors, leading to decrease in IL-6 signaling and reducing immune activation and inflammation.[35]

Given the central role IL-6 plays in CRS and since its earliest reported use in successfully dampening severe CRS in a pediatric CART recipient,[36] the IL-6 antagonist tocilizumab represents an important therapy for CRS. It was approved by the FDA for the treatment of severe or life-threatening CART-cell-induced CRS in adults and pediatric patients ≥2 years old.[37] Tocilizumab was later shown to reduce fevers and CRS symptoms without affecting CART levels in serum or bone marrow.[24]

Corticosteroids

Systemic corticosteroids are effective in dampening CRS due to its established anti-inflammatory properties. Due to early concern about steroids inhibiting CART activity and expansion,[24] its use early in CRS onset was relatively restricted in an effort to preserve CART anti-tumor activity. Typically, corticosteroids are reserved for cases of

Table 2 Selected CAR-T Trials Reporting CRS Incidence, Grading And Treatment

Trial	Publication Type	CRS Incidence (All Grades)	CRS Grade 3–4	CRS Grading Scale Used	Tocilizumab/ Corticosteroid Usage*
ZUMA-1[1]	Manuscript	94%	13%	Lee Criteria	43%/27%
JULIET	Manuscript[2]	58%	22%	UPenn	15%/11%
	Abstract[32]	57%	17%	Lee Criteria	
NHL 001[73]	Abstract	35%	1%	Lee Criteria	21%/21%
BB2121[4]	Manuscript	76%	6%	Lee Criteria	21%/12%
Axi-cel Real world experience[74]	Abstract	92%	7%	Lee Criteria	62%/57%

Note: *Corticosteroid usage for CRS, ICANS or both.

CRS refractory to tocilizumab, or being administered concomitantly with tocilizumab for high-grade CRS or CRS that occurs with associated neurotoxicity.[10]

Preliminary data suggest using IL-6 receptor blockade and/or steroids do not result in higher rates of relapse.[38,39] Moreover, prolonged steroid use (beyond 7 or more days) does not appear to adversely affect CART outcomes.[40] These findings have helped consider intervening with tocilizumab plus corticosteroids earlier in the treatment course,[41] and even as a prophylaxis against CRS.[42] Yet, large prospective trials are certainly needed before widely adopting this approach.

Siltuximab

Siltuximab is a murine chimeric moAb which is an IL-6 antagonist. While currently not FDA approved for the treatment of CRS, several centers have reported prescribing it for CART-related CRS. According to a survey conducted by a special interest group, half of the respondents described using siltuximab to treat CRS, but all agreed that siltuximab should be considered for cases of tocilizumab-refractory CRS.[43] One potential benefit of siltuximab, from the mechanistic standpoint, is the resulting increase in IL-6 levels following tocilizumab administration due to IL-6R binding, as opposed to siltuximab which binds directory to IL-6.[44] This rise in IL-6 is thought to increase risk of neurotoxicity.[14] We believe that more data are needed to better define the role of siltuximab in the first-line CRS treatment setting.

Anakinra

Anakinra blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs. Currently, it is FDA approved for the treatment for rheumatoid arthritis.[45] Macrophage produced IL-1 has been linked with CRS and neurotoxicity from CART, hence suggesting a role for IL-1 blockade with anakinra.[14,46] Anakinra has been described to have a therapeutic effect in hemophagocytic lymphohistiocytosis (HLH)[47,48] although it has not been reported or studied in CAR T induced HLH/MAS.

Dasatinib

Dasatinib is a tyrosine kinase inhibitor approved for the treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive ALL. It also has other effects including suppressing T-cell activation and inhibiting T cell signaling kinases including Src, Fyn and Lc.[49]

These effects have been studied in two separate pre-clinical models with CD19 CART, both demonstrating dasatinib reversibly suppressing cytolytic activity, cytokine production, and CD4+ and CD8+ antigen-induced proliferation of CART cells containing either CD28 or 4-1BB costimulatory modules.[50,51] In addition, Weber et al demonstrated that not only can this dasatinib function-off state be sustained for several days without affecting T cell viability, but that it is dose dependent, allowing titration of dasatinib for partial or complete CART functional suppression. These pre-clinical findings are exciting and warrant prospective clinical trials to further investigate the role of dasatinib on CRS. Table 3 summarizes current clinic trials focusing on the treatment of CRS.

A3 Adenosine Receptor Agonists

A3 adenosine receptors are expressed on various immune cells and activation of A_3AR has been correlated with anti-inflammation[52] Binding of A_3AR with A_3AR agonists inhibit inflammatory cytokine production and release by inhibiting the production of inflammatory cytokines through downregulation of NF-κB, hence reducing production of pro-inflammatory cytokines including TNF-α, IL-1, and IL-6.[53,54] Highly selective A_3AR agonists such as namodenoson and piclidenoson could represent potential therapeutic options for CRS treatment, but require additional clinical investigation.[53]

JAK/STAT Inhibitors

IL-6 signaling occurs through two different mechanisms: via the higher-affinity membrane-bound receptor (classic IL-6 signaling) or via a soluble IL-6 receptor (sIL-6R; trans-IL-6 signaling). Both ultimately result in the activation of the JAK/STAT pathway. Ruxolitinib is a JAK/STAT pathway inhibitor that has resulted in a significant reduction of inflammatory cytokines in preclinical and clinical studies. It was investigated for prevention of CRS from a CD123-directed CART in an AML xenograft model. This pre-clinical model demonstrated not only the efficacy of ruxolitinib in prevention of CRS, but it did not appear to affect anti-tumor activity of the CD123-directed CART.[55] Itacitinib, another JAK/STAT pathway inhibitor selective for JAK1, is being studied in a phase 2 study for the prevention of CRS. Further research is warranted regarding the role of JAK/STAT inhibition in the management and prevention of CRS (Table 2).

Table 3 Current Clinical Trials For Prevention Or Treatment Of CRS

Trial Number	Study	Status	Inclusion Criteria	Intervention
NCT02906371	A Two Cohort Pilot Study of Tocilizumab Optimization Timing for CAR-T19-Associated CRS Management in Pediatric Patients With CD19 Expressing Relapsed/ Refractory B-cell ALL	Active, not recruiting Two cohorts, open-label, phase1/2 study	Pediatric patients aged 1–24 years with CD19 expressing relapsed/refractory B-cell ALL	Two cohorts defined based upon pre-infusion high versus low tumor burden: **1**. High tumor burden cohort (high risk of severe CRS) to receive earlier administration of tocilizumab for CRS **2**. Low tumor burden cohort (low risk of severe CRS) to receive standard timing of tocilizumab for CRS
NCT04048434	Effectivity of Extracorporeal Cytokine Adsorption (Cytosorb) as Additive Treatment of CAR-T Cell-Associated Cytokine Release (CRS) Syndrome and Encephalopathy Syndrome (CRES)	Not yet recruiting	Patients aged 18 or older who develop severe CRS (>3)/severe CRES (>3) and CRS/CRES onset <6 hrs.	Patients with severe CAR-T cell-associated CRS (defined as vasopressor dependent) will be treated with standard of care + cytokine adsorption (6 hourly for 24 hrs.).
NCT03696784	A Phase I Study of Autologous Activated T-cells Targeting the CD19 Antigen and Containing Inducible Caspase 9 Safety Switch (iC9-CAR19) in Subjects With Relapsed/Refractory B-cell Lymphoma	Recruiting Phase I	Patients aged 18 or older with relapsed or refractory B-cell Lymphoma	Patients who develop grade 4 CRS or grade ≥3 CRS or who develop grade ≥3 CRES or grade 2 CRES that is unresponsive to standard of care interventions will be given Rimiducid at 0.4 mg/kg.
NCT03016377	Administration of Autologous CAR-T Cells Targeting the CD19 Antigen and Containing the Inducible Caspase9 Safety Switch in Patients With (iC9-CAR19) Relapsed/Refractory ALL	Recruiting Phase I	Patients aged 3–70 years with relapsed or refractory B-cell ALL	Patients who develop grade 4 CRS or grade 2/3 CRS that is unresponsive to standard of care interventions will be given Rimiducid at 0.4 mg/kg.
NCT04071366	A Study of Itacitinib for the Prevention of Cytokine Release Syndrome Induced by Immune Effector Cell Therapy	Study to open in January 2020 Phase 2	Patients 12 years and older eligible to receive either tisagenlecleucel or axicabtagene ciloleucel for approved hematologic indications	Oral administration of itacitinib 200 mg once daily for 30 days for the prevention of CRS

Note: Source: from ClinicalTrials.Gov (accessed on October 1, 2019).

Lenlizumab

GM-CSF cytokine elevation was identified by both the MSKCC and UPenn groups as a cytokine with a large increase in severe CRS,[6,24] while GM-CSF elevation was also observed in the development of severe grade 3 or 4 neurotoxicity.[1] Lenzilumab is a human monoclonal antibody that neutralizes human GM-CSF. Preclinical studies showed prevention of CRS and reduction in neuroinflammation without affecting CD19-targeted CAR-T function and enhanced anti-tumor activity in vivo when compared to CD19-CART without lenzilumab.[56] A clinical trial of axicabtagene ciloleucel with lenziumab is anticipated.

Suicide Gene

One approach to manage refractory toxicities such as CRS is to encode a conditional safety switch which can be used to eliminate the CART cells thus abrogating its immune effects. Suicide genes are one way to encode this safety

switch into a CART. One of the best known safety switch mechanisms is the caspase 9 (iCasp9)/AP1903 suicide system. This system was first utilized in allogeneic stem cell transplantation, where exposure to rimiducid would eliminate iCasp9-expressing t cells, eliminating t-cell-mediated effects of graft-versus-host disease.[57–59] Preclinical studies demonstrate the efficacy of this system when encoded in CART.[60,61] Other suicide gene platforms are in development with safety switches such as EGFR[62] and CD20.[63]

Discussion

CART cell therapy represents a success for the treatment of relapsed and/or refractory B-cell NHL and B-cell ALL. Early clinical experiences with CART cell products followed by large multi-center clinical trials, leading to their approval for wide commercial use, have highlighted the unique resulting toxicities. Although there are only two CD19 CART cell commercial products available, additional CART cell products targeting other novel antigens are anticipated to enter into clinical practice in the near future.[64–66] Additionally, other T cell redirected therapies such as bi-specific T-cell-engaging antibodies (BiTEs) and TCR-gene therapies are also part of the emerging treatment landscape secondary to the common underlying principle of immune effector cell activation causing tumor cell death.[67–69]

A thorough understanding of the toxicities associated with these highly effective therapies is of paramount importance in advancing the field of cellular therapeutics. CRS is one the main toxicities associated with CART cell therapy.[33] The underlying pathophysiology of CRS involves a supra-physiologic response of the immune system secondary to the activation of T cells, which further results in release of a multitude of cytokines and chemokines.[70] This is reflected in the current definition of CRS proposed by ASTCT and applies to not only CART cell therapy but to any therapy using immune effector cell activation as its primary mechanism of action.[10] As described above, signs and symptoms of CRS can be extremely variable ranging from mild symptoms to those requiring ICU care with cardiorespiratory support.[30] The lack of specificity of CRS presentation requires exclusion of other clinical situations that may mimic CRS. Infection and sepsis, for example, may present with fevers, hypotension, and other signs and symptoms similar to CRS. It is recommended that workup for CRS entails a thorough investigation to exclude infectious etiology, including cultures, imaging and/or initiation of broad spectrum antibiotics whenever clinically indicated. Also, CRS can share many overlapping features with HLH/MAS such as elevated ferritin and C-reactive protein.[1,6,33] This is not surprising given that both share the same underlying physiology of immune activation. However, features suggestive of HLH/MAS generally resolve with the resolution of CRS and it is therefore considered as part of the spectrum of CRS and not a separate entity.[10]

Early identification and accurate management is crucial in the treatment of toxicities associated with immune effector cell activating therapy. In this regard grading systems have been of vital importance and have evolved significantly from the original use of CTCAE v3 in early clinical trials to the current ASTCT consensus grading.[10] The important features of the ASTCT consensus include elimination of laboratory parameters as a part of grading system given the lack of specificity of most biomarkers; and the difficulty in obtaining results in real-time.

The importance of supportive care in the management of patients with CRS cannot be undervalued. Close monitoring by experienced nursing staff who are well informed of the current grading systems is crucial. To date, the most commonly used therapy for systemic treatment of CRS remains tocilizumab. Multiple studies confirmed the correlation of peak IL-6 levels with the severity of CRS and this led to the approval of tocilizumab for treatment of CRS concurrent with the approval of tisagenlecleucel.[23,24] The timing of administration of tocilizumab remains an area of debate. Initial clinical experience reserved tocilizumab to patients manifesting severe CRS.[36] With increased clinical experience and reports showing no significant compromise on the efficacy of CART, we are now seeing a shift in clinical practice where tocilizumab is being prescribed earlier in the course of CRS.[1,71] This is a practice approach which is also being supported by recent ASTCT guidelines.[10] This is similar to the experience with use of corticosteroids where the impact on CART efficacy is of less concern nowadays.[24,65,72]

CART therapies have produced dramatic results and they will continue to change the therapeutic landscape of oncology practice. Further refinement of existing strategies and development of new therapies to prevent and treat unique and potentially life-threatening toxicities such as CRS will be important to ensure this treatment can be safely administered to patients everywhere.

Disclosure

Professor Mohamed A Kharfan-Dabaja reports consultancy for Daiichi Sankyo and Pharmacyclics, outside the submitted work. Julio C Chavez reports consultancy for Kite/Gilead and Novartis and consultancy for Genentech, Bayer, and Karyopharm and speaker Bureau for Genentech. The authors report no other conflicts of interest in this work.

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