INTERNATIONAL MYELOMA FOUNDATION

Relapsed/Refractory Multiple Myeloma: The Potential of Anti-B Cell Maturation Antigen Therapy and Management Strategies

Discussion with IMF Nurse Leadership Board

September 6, 2019
Hoboken, New Jersey

IMF NURSE LEADERSHIP BOARD

INTERNATIONAL MYELOMA FOUNDATION

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IMF NURSE LEADERSHIP BOARD

Overview

On September 6, 2019, 10 members of the International Myeloma Foundation (IMF) Nurse Leadership Board convened in Hoboken, New Jersey, for their annual meeting to discuss the potential of anti-B cell maturation antigen (BCMA) in patients with relapsed/refractory multiple myeloma (RRMM) and to discuss challenges in patient management.

The objectives of the discussion were to

1. Obtain insights on updated bb2121 (also known as idecabtagene vicleucel or ide-cel) clinical and safety data
2. Understand management strategies for adverse events
3. Identify challenges of short-term and long-term patient management
4. Understand unmet needs of oncology nurses as well as types of support and resources needed

Introduction

Multiple myeloma (MM) is a relatively uncommon cancer that develops in plasma cells found in the bone marrow. These plasma cells are an important part of the immune system. The abnormal growth of plasma cells can lead to low blood counts, bone and calcium complications, kidney damage, and higher susceptibility to infections.[1]

Worldwide, there were approximately 138,000 incident cases of MM and an associated 98,000 deaths in 2016. Between 1990 and 2016, new cases and related deaths increased by 126% and 94%, respectively. East Asia had the largest increase in incident cases over this time, and Australasia, high-income North America, and Western Europe had the highest age-standardized incidence rates of MM.[2]

In the United States, an estimated 32,000 new cases of MM and 13,000 related deaths are expected in 2019. The proportion of newly diagnosed MM cases increases with age, peaking for the group aged 65-74 years and then decreasing thereafter (Figure 1). The median age of diagnosis is 69 years. In addition, higher rates of MM occur in men than women and those of African American descent than other races.[3]

More than 50% of patients with MM survive at least five years after diagnosis,[3] in large part due to advancements in the diagnosis, treatment, and management of patients over the last decade.[4] Despite these improvements, MM remains incurable and novel treatment strategies are needed.[5] One novel approach using genetically modified T-cells offers promising early clinical trials results for patients with RRMM.[6,7]

Chimeric antigen receptor T-cell (CAR T-cell) therapies are adoptive immunotherapies that use genetically engineered autologous T lymphocytes to target specific antigens expressed on cancer cells, independently of

major histocompatibility complex expression.[5] Recently, CAR T-cell therapies are being investigated in patients with hematologic malignancies, including acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), lymphomas, and MM.[5,8]

Since 2017, the Food and Drug Administration (FDA) has approved two anti-CD19 CAR T-cell therapies for patients with leukemia and lymphoma. Kymriah (tisagenlecleucel) is FDA-approved to treat children and adults with relapsed or refractory B-cell ALL and adults with relapsed or refractory large B-cell lymphoma.[9] Yescarta (axicabtagene ciloleucel) is FDA-approved to treat adults with relapsed or refractory large B-cell lymphoma.[10]

Another CAR T-cell therapy currently undergoing study is idecabtagene vicleucel (ide-cel; bb2121). This investigational therapy targets B-cell maturation antigen (BCMA), a protein within the tumor necrosis factor superfamily expressed on malignant and normal plasma cells and mature B cells. Outcomes in heavily pretreated patients is especially of interest, given that most patients with MM will experience relapse and require additional therapy. Despite improvements in median survival with immunomodulatory drugs and proteasome inhibitors, overall survival is just 13 months for patients who have received at least three prior lines of therapy, become refractory to immunomodulatory drugs and proteasome inhibitors, and who have been exposed to an alkylating agent.[11]

In the open-label, multisite phase 1 study of ide-cel in patients with RRMM (NCT02658929), the results of the first 33 consecutive patients have been reported. All patients had received at least three prior lines of therapy. In the dose-escalation cohort, patients had received a median of 7 previous treatment regimens, and in the expansion cohort, patients received a median of 8 previous regimens. All patients except one had received autologous stem-cell transplantation, and all patients received both bortezomib and lenalidomide previously. A total of 79% (26/33) were exposed to bortezomib, carfilzomib, daratumumab, lenalidomide, and pomalidomide; 18% (6/33) were refractory to these agents; 79% were refractory to both a proteasome inhibitor and an immunomodulatory agent. During the manufacturing process, 42% received bridging therapy, most commonly dexamethasone, daratumumab, bortezomib, and bendamustine[7]

Patients received lymphodepleting chemotherapy of fludarabine and cyclophosphamide and one infusion of ide-cel. In the dose-escalation phase, 21 patients received 50 x 10^6, 150 x 10^6, 450 x 10^6, or 800 x 10^6 CAR T-cells. In the dose-expansion phase, 12 patients received 150 x 10^6 to 450 x 10^6 CAR T-cells. All patients were followed until disease progression. Safety was the primary endpoint, and adverse events were graded according to

National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[7]

After a median follow-up of 11.3 months, 85% of patients (28/33) had an objective response, with 9% having a complete response and 36% having a stringent complete response. Objective responses were observed across all doses of CAR T-cells, though the frequency and duration of response occurred in a dose-dependent manner. Objective response rates were 33%, 75%, 95%, and 100% for patients who received 50 x 10^6, 150 x 10^6, 450 x 10^6, or 800 x 10^6 CAR T-cells, respectively. Response rates were similar, independent of BCMA expression or previous treatment exposure.[7]

Overall, the first partial response or better to ide-cel occurred early after infusion, with a median time to response of 1.0 month. The median progression-free survival was 11.8 months for patients who received ≥150 x 10^6 CAR T-cells compared with 2.6 months for those who received <150 x 10^6 CAR T-cells. Among the 18 patients that were evaluable for minimal residual disease (MRD), 16 patients had a partial response or better and 2 patients did not have a response. The 16 patients with a response were MRD-negative at 10^{-4} nucleated cells or better, 15 of 16 were negative at 10^{-5} cells, and 3 were negative at 10^{-6} cells. Negativity was observed at the first assessment, and 12 patients were MRD-negative on at least two assessments. The 2 patients without a response were MRD-positive in the first month.[7]

For all dose levels greater than 50 x 10^6 CAR T-cells, the expansion of ide-cel was observed in vivo. CAR T-cell expression was durable, persisting in 96%, 86%, 57%, and 20% of patients after 1, 3, 6, and 12 months, respectively.[7]

Adverse events were reported for all patients, with 97% (32/33) having grade 3 or higher toxicities. The most common grade 3 or higher adverse events were hematologic effects, including neutropenia (85%), leukopenia (58%), anemia (45%), and thrombocytopenia (45%). Other grade 3 or higher non-hematologic events were not common. Cytokine release syndrome (CRS) was reported in 76% of patients (25/33), with grade 1 CRS or grade 2 CRS in 70% of patients and grade 3 CRS in 6%. CRS occurred with a median onset of 2 days and a mediation duration of 5 days. CRS was treated with tocilizumab in 7 patients and glucocorticoids in 4 patients. CRS correlated with CAR T-cell dose, occurring more frequently in those who received >150 x 10^6 CAR T-cells than those who received ≤150 x 10^6 CAR T-cells. Neurologic toxicities were reported in 14 patients (42%), with 13 patients having grade 1 or 2 effects and 1 patient had a grade 4 neurotoxicity 11 days post-infusion that resolved within 1 month. Fourteen patients (42%) developed an infection, with one grade 3 anal abscess and one grade 3 parvovirus infection.[7]

In heavily pretreated patients with RRMM, ide-cel is proving to be a promising treatment option with an early and dose-dependent objective response across all doses of CAR T-cells.[7]

The IMF Nurse Leadership Board's discussions focused on CAR T-cell therapy coordination and management of this therapy and its toxicities. The Board also discussed long-term follow-up care and the need for adequate infrastructure stabilization when ide-cel becomes FDA-approved for patients with RRMM.

CAR T-Cell Therapy Management Strategies

CAR T-Cell Therapy Coordination

Successful CAR T-cell therapy programs will require multifaceted coordination and support (Figure 2). Should ide-cel reach regulatory approval, adequate infrastructure will be needed to manage the influx of patients expected to want this therapy. Additional infrastructure is needed to manage CAR T-cell therapy-specific adverse effects, such as CRS and neurotoxicity. While some institutions have established cellular therapy programs, other institutions will need assistance in setting them up. In places without established cellular therapy teams, responsibilities for patient management fall to different divisions and providers need clarity on how to delegate responsibilities. Providers need a dedicated specialist to set up such programs and provide ongoing training to staff.

Nurses remain key providers in managing all aspects of the treatment process. Management of CAR T-cell therapy toxicities will be an important component of the overall treatment plan moving forward. Patients, caregivers, and providers will need assistance with managing toxicities as well as long-term follow-up care.

Managing Patient Expectations

Many patients have a high expectation of cure with CAR T-cell therapy. Both physicians and nurses need to set the patient's expectations to reflect the nature of myeloma disease biology and the end goal is longer remission. Nurses familiar with the clinical trial data will need to manage patient excitement associated with this therapy. "*We've set the expectation to the patient that they're going to be very successful. Sometimes, we have to say, 'Yes, we want to try it,' and 'Yes, we hope that it keeps you in a remission much longer*." – *Nurse leader*

Nurses and other providers need to have an understanding that not all patients will qualify for treatment with CAR T-cell therapy. While the phase 1 trial of ide-cel included relapsed and refractory patients who had previously received multiple lines of therapy,[7] some patients were too frail or too ill from disease-related complications to qualify for treatment. Not qualifying for therapy may be a disappointment to some

patients who place a lot of hope in trying this therapy, and nurses need to have frank discussions with patients about whether or not they will qualify. In some cases, if performance status is poor due to progressive disease, patients may be a candidate and benefit from this therapy, highlighting the importance of proper patient selection. "*You have to have the conversation earlier, rather than later, with this type of cellular therapy, because patients can be frail from the disease and beaten down by chemotherapy side effects, too*." *– Nurse leader*

At least one ongoing trial is studying the use of ide-cel earlier in the course of the disease (NCT03651128).

Bridging Chemotherapies

Bridging chemotherapy might be required following T cell apheresis and prior to the CAR T-cell infusion.[12] Bridging chemotherapy can control MM and minimize organ toxicity, until the completion of the CAR T-cell manufacturing process.[13] Currently, there is no standard treatment regimen for bridging chemotherapy prior to CAR T-cell therapy in MM, and only some patients will require bridging chemotherapy. Selecting an appropriate bridging therapy is challenging when patients have relapsed on prior therapies. Prior combinations that patients responded to in the past may be tried again. However, treatment regimens are different for all patients, and questions remain as to what bridging therapy is best for patients. "*It's a work in progress as far as bridging therapy goes*." *– Nurse leader*

Current clinical data support that more patients respond to CAR T-cell therapy when they have received bridging therapy. Lessons learned from the phase 1 trial of ide-cel suggest that bridging therapy may be needed in some patients and promotes a better response. Active disease must be present prior to the administration of lymphodepleting chemotherapy and CAR T-cells. In the trial, patients who had received bridging therapy had a 100% objective response rate, compared with a 74% objective response rate in those who had not received bridging therapy.[7]

Premedications and Prophylaxis

Patients who will receive CAR T-cell therapy need to have specific precautions in place to encourage the best response with therapy. For example, corticosteroids should be stopped to allow for an appropriate washout period prior to starting CAR T-cell therapy. Steroids can be safely given for a limited course of treatment for CRS or neurotoxicity.[14] Infection prophylaxis is another important consideration during both bridging therapy and infusion. CAR T-cell therapy should be delayed until infection is cleared or ruled out. In patients with CRS, undiagnosed infections can lead to mortality, likely due to exacerbation of the systemic inflammation from infection.[14]

Potential solutions that may reduce some of the challenges associated with patient management include

- Avoiding the use of corticosteroids and using the electronic medical record (EMR) to signify that patients receiving CAR T-cell therapy should avoid their use.
- Convening with the infectious disease department to develop a prophylaxis protocol.
- Initiating infection prophylaxis (antiviral, antibacterial, and antifungal) as appropriate.
- Utilizing syndromic testing systems to identify pathogens and determine the best course of treatment.
- Delaying CAR T-cell therapy if an infection is suspected at the time of infusion.
- Developing guidelines for re-vaccination and encouraging family members and caregivers to receive appropriate vaccinations (i.e., influenza and shingles vaccines) while caring for patients.

Toxicities with CAR T-Cell Therapies

There are known toxicities associated with CAR T-cell therapies. In some cases these may be serious and potentially life-threatening.[15] Two of the most common adverse events associated with CAR T-cell therapy are CRS and neurotoxicity.[14] CRS is a systemic inflammatory response that can lead to widespread, but usually reversible, organ dysfunction from excessive cytokines released into the system. Neurotoxicities can include headaches, delirium, tremor, loss of consciousness, and seizures. Tocilizumab, an anti-interleukin-6 receptor antibody, is a mainstay treatment for CRS, and corticosteroids are suitable to manage neurologic toxicities and CRS not responsive to tocilizumab.[15] Patients treated with CAR T-cell therapy will require intensive monitoring and immediate management of toxicities, as some may need emergency care and/or hospitalization for monitoring.

Despite the potential severity of adverse effects, consensus guidelines are lacking for the clinical management of CAR T-cell associated toxicities. The American Society for Transplantation and Cellular Therapy (ASTCT) grading system is a commonly used grading system (Tables 1 and 2).[16] However, assessment and management of toxicities still varies by institution. The ASTCT is developing management guidelines, but they will differ based on the product administered and patient characteristics. One challenge lies in coordinating care with community providers and helping to educate them on best practices for managing toxicities. As such, nurses and other providers need a unified system for grading and treating CAR T-cell toxicities. Many nurses have used the Cartox smartphone application to aid in toxicity grading and treatment. The ASTCT smartphone application is also now available for toxicity grading.

Whether toxicities are managed in the inpatient or outpatient setting varies by institution. However, CRS and neurotoxicity are typically managed in the inpatient setting. Determining code status is an important consideration for patients who are treated with CAR T-cell therapy, as severe toxicities may require intensive care. Patients and caregivers must be educated about adverse events and provided with written information about who they should contact in case of an emergency.

Cytopenias

Cytopenias, or lower-than-normal numbers of blood cells,[17] commonly occur with MM therapies.[18] No current standards or guidelines exist for the frequency and duration of monitoring of cytopenias. Institutions vary on whether growth factors are used to treat cytopenias, and in many cases, the decision to use growth factors is provider-driven. "*We give it liberally at our institution...Because we're sending patients home to their outpatient provider, and we want coverage. It's an insurance policy, basically, that they will not be neutropenic for a period of time until they can safely get into established care*." *– Nurse leader*

B-Cell Aplasia and Hypogammaglobulinemia

CAR T-cell therapy targets cancerous B cells, as well as healthy B-cells, and can lead to B-cell aplasia, or depletion, resulting in chronic immunodeficiency. B-cell aplasia can lead to hypogammaglobulinemia, or low levels of antibodies in the blood, which places patients at an increased risk of infection.[17, 19] Though not enough evidence is available to quantify the proportion of patients who will develop hypogammaglobulinemia with BCMA-targeted CAR T-cell therapy, hypogammaglobulinemia can occur in approximately 40% of patients following CD19-targeted CAR T-cell therapy.[19] As such, many institutions treat this condition with intravenous immunoglobulin (IVIG).[17]However, no current standards exist for the criteria at which to initiate treatment, the frequency of infusion, or the duration of repletion and the decision to use IVIG is often provider-driven. "*We tend to give it [IVIG] monthly for at least 2 months and then see how the patients are. There's a lot of people in our practice that use it ongoing because there are a lot of different physicians, and everybody has their different perspective*." *– Nurse leader*

Psychosocial Changes

Patients require psychological long-term follow-up and psychosocial issues should be addressed at each visit during disease monitoring. Patients can sometimes have unanticipated psychosocial changes after CAR T-cell therapy and experience a type of withdrawal from the regularity of treatment and support from providers if in remission. This aspect is unique to patients treated with CAR T-cell therapy because often no treatment is needed post-therapy if a patient responds. "*Patients are going from treatment after treatment, and then all of a sudden they're on nothing afterward. It's*

that living and waiting for the other shoe to drop." – *Nurse leader*

Many patients have anxiety about relapse and constantly ask about the next treatment option. Nurses and other providers need to assess quality-of-life and distress scores at every patient encounter.

Caregiver Support and Logistical Issues

Family and caregiver support plays a large role in managing toxicities and patients are dependent on them for certain aspects of care, such as transportation to follow-up services. The support of the caregiver is critical and continual, and ongoing support may be an emerging issue for some patients if ide-cel is commercially available. Institutes that use CAR T-cell therapy mandate a dedicated support person, who must be available 24 hours a day for the first 30 days post-CAR T-cell therapy. If the patient does not have a dedicated caregiver, sometimes insurance will pay for a hired caregiver.

Transportation and proximity to treatment centers can be a challenge for patients. Reliable transportation to and from treatment and follow-up care is necessary, as caregivers are asked not to drive for the first month post-CAR T-cell therapy. Some institutions require that patients be within 60 miles or a one-hour drive from the treatment center. Housing during and after treatment can also pose a challenge. Patients are advised to stay close to the treating institution if possible. While some clinical trials support a stipend for housing, most insurance plans will not cover the cost. For some patients, the selection of one treatment hospital over another may be driven by the affordability of housing during treatment.

Long-Term Follow-Up

Post-hospital care and follow-up processes differ by institution, oftentimes dependent on whether the patient receives care at an academic or community setting. The relationship between providers at academic institutions and community oncologists is critical to the patient's long-term monitoring plan after treatment. An informational packet should be created for patients to share with their oncologist and/or primary care provider. This packet should outline the posthospital care needs of CAR T-cell therapy patients, including directives to call the oncologist or managing the healthcare team if toxicities arise post-CAR T-cell therapy.

If patients experience adverse events outside of regular clinic hours, the patient should return to the academic institution's emergency room (ER). However, challenges may exist for ER staff who may not be trained in the management of CAR T-cell therapy-specific toxicities. The EMR needs to flag patients receiving therapy and indicate any precautions (i.e., steroid avoidance). Patients, caregivers, and providers need ongoing education on the signs and symptoms that would necessitate care or an ER visit. Long-term follow-up for patients who receive these therapies is

mandated by the FDA for 15 years, and subjects will need long-term follow-up for adverse events and second malignancies.[20]

Education Needs of Patients and Providers

Patient and Caregiver Education Needs

A MM diagnosis can be overwhelming for patients and their caregivers. However, a streamlined approach that uses patient-friendly materials can help reduce the fear and anxiety with treatment and also provide direction to patients should they experience any toxicities and adverse events. Nurses need to be armed with specific resources that outline the treatment journey for patients (Table 1). Nurses, case managers, pharmacy staff, CAR T-cell coordinators, and physicians all provide education to patients and caregivers. The education tools may be in the form of an online portal, pamphlets, or other highly visible tools, such as a refrigerator magnet or calendar. Materials should include information about potential toxicities and adverse effects, especially signs and symptoms that would necessitate emergency care, the role of the caregiver, a timeline for treatment duration, and reminders for appropriate follow-up care. Patients and caregivers are mandated to attend educational classes to understand treatment calendars and adverse events.

Provider Education Needs

Providers' educational needs are similar to those of patients and caregivers (Table 3). As CAR T-cell therapy is an emerging therapy, many clinicians may be unfamiliar with how to manage CAR T-cell toxicities. This is especially the case in community hospitals or rural settings, where providers may not manage many MM patients, or they are not utilizing investigational agents such as ide-cel. Resources, such as a phone hotline for primary care providers, would be extremely useful in these scenarios. Even within academic institutions, staff that do not normally manage patients with MM require additional education, such as those staff in the ER who may not be trained on CAR T-cell therapy-specific toxicities. Administrators should also be educated on management, including the cost of care relative to other standard-of-care modalities. Educational tools should include both traditional and electronic tools; streamlined information, such as a CAR T-cell therapy information card, needs to be developed and can mirror cards already developed for other approved therapies.

Commercialization of Ide-cel

FDA approval of ide-cel will provide opportunities to improve standard-of-care practices for patients who often have tried several other lines of therapy. However, institutional and large-scale commercialization challenges will remain for production capacity of this and other CAR T-cell therapies.[21]

For instance, institutions may face space limitations and delays in admitting patients when managing adverse events.

Additionally, apheresis and processing areas continue to be a bottleneck in the patient treatment journey because of scheduling challenges. Thus, manufacturing delays could represent a real challenge if ide-cel becomes commercially available. Institutional storage capacity for cells will likely also be a logistical issue in the future, as the need for storage will change over time. Institutions are encouraged to learn from existing lymphoma and leukemia CAR T-cell therapy programs to successfully manage these challenges moving forward.

Closing Statements

CAR T-cell therapy represents a promising cellular immunotherapy to treat patients with RRMM, especially in those who have received several lines of therapy previously.[7]

Due to the novelty of this therapy for patients with RRMM, there are complexities surrounding therapy coordination and ongoing management of toxicities and follow-up care. Once ide-cel reaches regulatory approval, logistical challenges will need to be carefully navigated to make this therapy commercially available to all eligible patients.

Given the increased interest in the use of CAR T-cell therapy for patients with RRMM, all providers who interact with patients during the CAR T-cell therapy process and after discharge must be properly trained. This is essential to ensure the best clinical outcomes for patients. Nurses must continue to provide the necessary education to properly inform patients and caregivers about this treatment option and its toxicities.

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Figure 1. Percent of New Cases of Multiple Myeloma by Age Group [3]

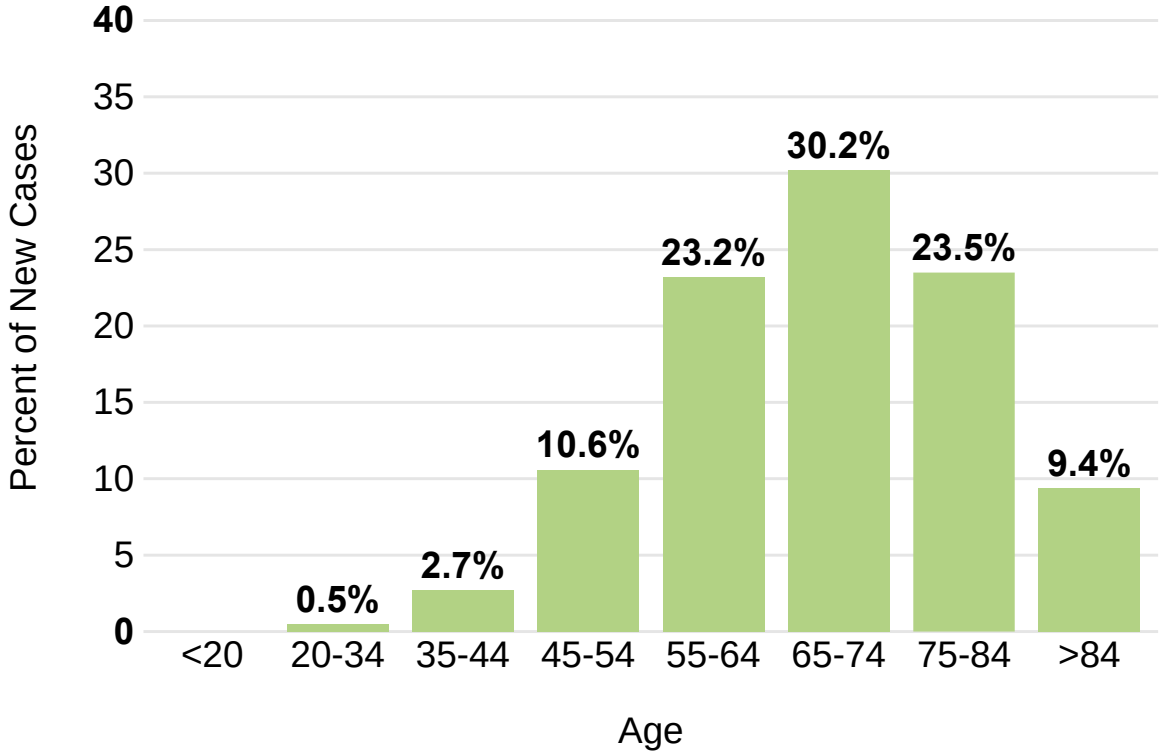

Figure 2. Cellular Therapy Coordination

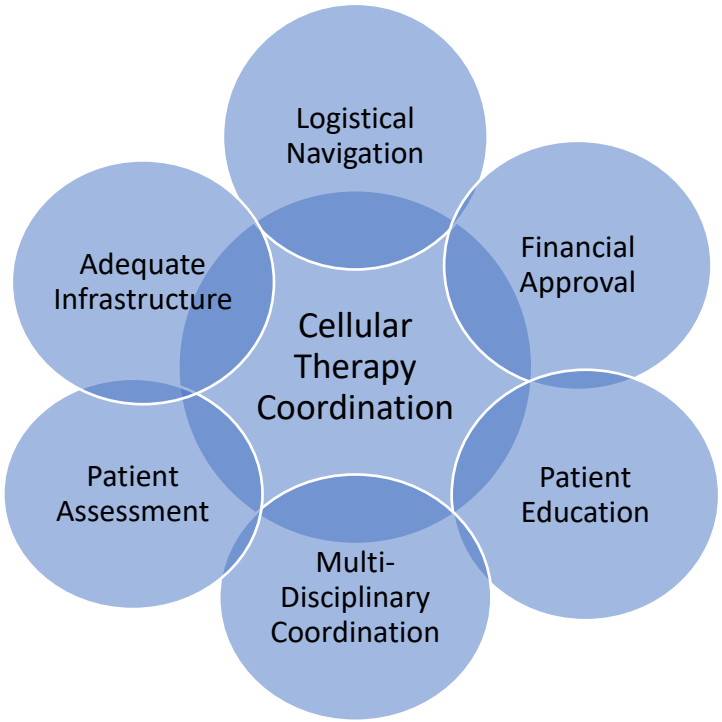

Table 1. ASTCT CRS Consensus Grading[16]

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	Nor requiring vasopressors	Requiring a 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 antipyretic 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 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

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

The information contained in this table was originally presented in: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome

Table 2. ASTCT ICANS Consensus Grading for Adults[16]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed Level of Consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient in unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor Findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing, or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

The information contained in this table was originally presented in: Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; EEG, electroencephalogram; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; N/A, not applicable

Table 3. Proposed Tools and Resources for Patients, Caregivers, and Providers

Tools and Resources for Patients and Caregivers
An online portal, containing information on potential toxicities (especially signs and symptoms that would necessitate care or emergency care), the role of the caregiver, treatment duration and reminders.
A written pamphlet that redirects patients to online resources, which should be regularly updated.
A CAR T-cell therapy information card, outlining the treatment process, treatment duration, potential toxicities, and assessing symptoms after treatment. This information should not be fused with allogeneic or autologous stem cell transplant information.
A treatment calendar or schedule that outlines a timeline and treatment duration.
A written guide on the role of the caregiver, including treatment calendars and support post-therapy for transportation to follow-up services and recognition of potential toxicities that warrant additional care.
A refrigerator magnet listing the signs and symptoms of toxicities and a contact number for the healthcare team if needed.
A packet for patients who are treated in a community setting or rural area to share with their oncologist and/or primary care provider with directives to call the oncologist or managing healthcare team if issues arise post-CAR T-cell therapy.
Tools and Resources for Providers
A CAR T-cell therapy information card, outlining the treatment process, treatment duration, potential toxicities, and assessing symptoms after treatment.
A phone hotline for primary care providers to ask questions about toxicities or management post-therapy.
A booklet or pamphlet outlining the treatment process, treatment duration, potential toxicities, and follow-up.
A guide for administrators on CAR T-cell therapy costs and standard-of-care costs.
Guidelines and consensus on existing guidelines for CAR T-cell therapy-associated toxicities, similar to what has been established for transplant.
Templates for grading CRS and neurological toxicities for nurses.
Smartphone applications, such as Cartox, to aid in grading and treatment of toxicities.
Global alerts within electronic medical records to signify medications that patients receiving CAR T-cell therapy need to avoid.

CRS, cytokine release syndrome