Original Article

Management Of Emergency Adverse Effects Of Cart Cell Therapy In Hematologic Cancers

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Abstract

Hematological cancers, such as lymphoma and leukemia, have been successfully treated with Chimeric antigen receptor (CAR) T cells. Several CAR T-cell medicines have already received approval, and more are being tested with similar indications or expanded to treat other cancers. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are possible serious or even fatal complications of CAR T-cell therapy. Due to this, medical emergency teams (MET) are being called upon more frequently to evaluate and treat CAR T-cell consumers. To provide METs a survival manual with a suggested care protocol, this article highlights the main problems and therapeutic procedures that follow the fundamental CAR T-cell therapy principles.

Introduction

CAR T-cells are T lymphocytes that have undergone genetic engineering to create a particular T-cell receptor. The Food and Drug Administration (FDA) granted their initial confirmation for relapsed B-cell acute lymphoblastic leukemia (B-ALL) in adolescents and diffuse large B-cell lymphoma (DLBCL) for adults in 2017. CARs have gone through numerous phases of gradual development (1). The special benefit of this approach is that, in contrast to natural T cells, CAR T-cells may identify antigens without the MHC presenting them. To further enable immune activation, tumor cell detection, and elimination, the chimeric receptor is capable of activating T cells as well as binding to antigens. In essence, T cells are extracted from the patient's blood or that of a healthy donor, modified by genetic to produce a particular CAR, and subsequently injected to the subject (2). Patients frequently get chemotherapies to reduce lymphocytes prior to infusion, with fludarabine and cyclophosphamide being the most prevalent ingredients (3). This encourages the adoptively injected T-cells to expand preferentially over innate lymphocytes. To prevent the eradication of healthy cells, the targeted antigen is mainly particular to cancerous cells. As soon as the CAR T-cells recognize the desired antigen, they are immediately activated and multiply in vivo to combat cancer (4).

Seven CAR-T treatments for hematological malignancies had received global approval as of March 31, 2022. Despite being a successful treatment for many cancers, CAR-T therapy has drawbacks. When CAR-T cells are infused, the incidence of CRS, the most frequent adverse event, can reach 93%. Along with cardiovascular, hematological,

hepatological, cutaneous, pulmonary, and gastrointestinal damage, CRS is the most important risk factor for ICANS. The broad use of CAR-T treatment is substantially hampered by severe adverse responses made worse by CRS (5).

The majority of CAR-T cell-induced complications (Table 1) might be handled if detected promptly, and CRS frequently co-occurs with other organ system toxicities. The difficulty in recognizing the organ system toxicity of simultaneous CRS, however, prevents prompt diagnosis and therapy. Therefore, in order to lower mortality and boost recovery rates, it is essential to have a thorough awareness of these side effects, associated risk factors, and therapeutic techniques for related complications (5).

Complication	**Primary symptoms**	**Association with CRS**	**Traits**
CRS	Hypotension; Toxicity across several organ systems, DIC	—	A widespread inflammatory response brought on by a variety of inflammatory causes
ICANS	Seizures, Brain edema	ICANS and CRS might come on together or not because CRS is one of the primary triggers of ICANS.	Pro-inflammatory cytokines and CAR-T cells enter the CSF through capillary permeability and BBB disruption, causing injury to the CNS.
Cardiovascular toxicity	Cardiogenic shock, Arrhythmia, Hypotension, QT prolongation	One of the primary causes of cardiovascular toxicity is CRS, which may result in severe, either direct or indirect cardiovascular consequences.	Cardiovascular damage may result from abnormally elevated inflammatory cytokines and off-target CAR-T cell reactions to actin.
HLH/MAS	Ferritin levels are very high, and High fever, Cytopenia, Coagulopathy	Since HLH/MAS is a severe form of CRS, it can be challenging to differentiate between the two.	Although HLH/MAS is uncommon, it has a high fatality rate and a poor prognosis.
Pulmonary toxicity	Failure of the respiration	One of the key factors that causes lung toxicity is CRS.	Regarding pulmonary toxicity, there are clear clinical diagnostic signs.

Complication	Primary symptoms	Association with CRS	Traits
Renal toxicity	Acidosis, electrolyte imbalances, failure of the kidneys, and inadequate adrenal function	One of the key factors that causes renal toxicity is CRS.	Regarding renal toxicity, there are clear clinical diagnostic signs. Symptomatic therapy is typically employed.

Table 1. Emergent complications of CAR-T cell therapy.

Emergent Adverse Events of CAR T cell therapy and Their Management

The care of patients who experience CAR T-related toxicities must include early identification and multidisciplinary therapy. A grade-based care strategy for CRS and neurologic toxicity is advised by the CARTOX group (Table 2) (6, 7, 8). These management guidelines state that supportive or pharmaceutical treatment could be used to treat lower-grade ICANS and CRS patients on the hospital's ward. Infections and other significant differential diagnoses must be ruled out while treating CRS and ICANS in their initial phases (grades 1-2). The early use of tocilizumab in patients with milder types of CRS might be increasingly thought of as routine care, even if the majority of patients react well to supportive therapies such as antipyretics and IV fluid resuscitation. Aspiration safety measures and swallowing evaluation are advised in relation to ICANS. Aspiration safety measures and a swallowing examination are advised in relation to ICANS. EEG and brain imaging, ideally MRI, should also be taken into account (9, 10). The use of preventive levetiracetam is advised without the occurrence of seizures (6, 10, 11). Nevertheless, neither the timeframe nor the dosage has been established. In general, it is essential for MET, hemato-oncologists, neurologists, along with other system experts to work closely together from the beginning (12).

ICU admittance requirements

Patients with higher (≥ grade 3) toxicities should often be handled in the intensive care unit (6, 7, 8, 13, 14, 15). Patients meet the requirements for ICU admission if they need one or more organs supported or if they have a lowered degree of awareness (7, 13); but according to a recently released study examining ICU therapy of CAR-T cell-associated complications, the majority of patients transferred to the ICU had CRS grades 1-2 (73%) and ICANS grades 2 (81%) at admission (16). According to this survey, reasons for disclosing lower-grade toxicities included worries about future worsening, the necessity for additional procedures, worries about developing noncardiogenic pulmonary edema, or the possibility of abrupt worsening as a result of a significant tumor load (7). Approximately thirty percent of the patients needed to be admitted to the ICU, all for ICANS, sepsis, or CRS, according to the CARTTAS trial looking at consequences in patients who received CAR-T cells (17).

Intensive care administration

Following the corresponding standard intensive care recommendations, supportive therapy for organ dysfunction or failure is used (18, 19). According to the CAR-ICU study, participating units' management approaches are quite comparable (16). Most units employ a repeating fluid bolus of 4 ml/kg for fluid management, and fluid responsiveness was evaluated using non-invasive techniques (stroke volume change, cardiac output, and ultrasonography-guided). Early evidence suggests that early vasopressor usage is preferable to overt hydration control for managing prolonged hypotension in CRS (7). Noradrenaline, vasopressin, and epinephrine are typically used as first-line vasopressors in medical facilities (16). The majority of facilities make a non-invasive ventilation attempt prior to intubation for patients with respiratory insufficiency (16). A cardiac examination, including cardiac biomarkers or the execution of

an echocardiogram, is advised in individuals with protracted severe CRS (10). Along with neuroprotective assessments, more intrusive intracranial pressure measuring and improved neuroprotective therapy may be required for individuals with neurotoxicity (6, 8, 20). Benzodiazepines and supplementary antiepileptic medications, especially levetiracetam, should be used to treat both nonconvulsive and convulsive status epilepticus. Phenobarbital should come next (6). Assessment for infections and starting broad-spectrum antibiotics must be taken into consideration because sepsis upon ICU admission may be a significant factor in determining mortality in this group of patients, especially if they are neutropenic (17).

Specific treatments

Corticosteroids inhibit the immune system and are useful in the treatment of CRS and ICANS (13, 18, 21). The preferred course of treatment is IV corticosteroids for ICANS ≥ grade 2 sufferers (22), while in CRS, they are utilized as a last resort in cases of recalcitrant symptoms. Recent guidelines have indicated that steroids be added in cases of severe CRS that did not react to the initial dosage of tocilizumab (10); nevertheless, the proof for this is weak, and each case must be analyzed separately. Steroids such as methylprednisolone or dexamethasone are frequently utilized for both CRS and ICANS. In order to avoid endangering CAR-T cell functioning, steroid usage was initially limited to patients with CRS unresponsive to anti-IL6 therapies or patients with grade 3-4 CRS toxicities (6). Nowadays, this concern has proven to be unfounded (20, 23, 24). Whenever CRS symptoms improve, steroids should be appropriately taken off (10).

The primary immunosuppressive medication for CRS is tocilizumab, an IL-6 receptor blocker (13). It binds the soluble as well as the cell-associated IL6 receptor. Tocilizumab has been shown in multiple studies to be beneficial for severe or fatal CRS, and most patients with CRS respond quickly to it—fever and hypotension frequently improve in a few hours (25, 26). Yet, pre-emptive or prophylactic use of tocilizumab has been considered, as inhibiting IL6 with tocilizumab neither significantly reduced curative effectiveness for CART cells nor negatively affected CART cell recipients' outcome (6, 23, 27, 28). Tocilizumab has been demonstrated to be unsuccessful in people with pure ICANS and should solely be used in patients with simultaneous CRS (22, 29, 30). This could be because tocilizumab cannot penetrate the BBB (13); however, IL6 is believed to be involved in the pathophysiology of CAR T-related neurotoxicity, and blood levels of IL6 have been observed to rise temporarily after tocilizumab delivery, potentially leading to worsening of neurological symptoms (13).

Siltuximab is a direct IL6 antagonist with comparable effects to tocilizumab. Siltuximab may be beneficial in the setting of passive distribution of IL6 to the CNS; nevertheless, a prospective and randomized evaluation between siltuximab and tocilizumab is still lacking, and siltuximab is still being evaluated by the European and US drug organizations (6).

Third-line medications have been recommended for therapy-resistant CRS (10); These medicines, however, are currently deemed experimental. Whereas IL6 inhibition primarily prevents CRS, anakinra's added IL1 blocker may protect both CRS and ICANS (29). The latest study revealed that anakinra might serve as a promising steroid-free solution for CAR T-cell therapy-related toxicities, including ICANS. Numerous investigations are underway to explore it's early and/or preventive use (31).

Grade	Manifestation	Recommendations
Grade 1	Organ toxicity, fever	✓ Acetaminophen and a blanket to regulate body temperature when treating fever ✓ If it's not contraindicated, ibuprofen can be taken as a second alternative for treating fever. ✓ Perform chest imaging and urine and blood tests to check for infections.

Grade	Manifestation	Recommendations
		✓ If neutropenic, empirical broad-spectrum antibiotics like filgrastim ✓ Symptomatic therapy of organ toxicity and constitutional symptoms; maintenance of IV fluids for hydration; ✓ Employ siltuximab 11 mg/kg IV or tocilizumab 8 mg/kg IV if the fever is prolonged (lasting for more than three days) and unresponsive.
Grade 2	Hypotension	✓ A 500–1,000 ml bolus of normal saline intravenous fluid ✓ If the systolic blood pressure stays below 90 mmHg, a second IV fluid bolus may be administered. ✓ Siltuximab 11 mg/kg IV or Tocilizumab 8 mg/kg IV is used in the management of hypotension that is resistant to fluid boluses; tocilizumab can be given after six hours if necessary. ✓ Systolic blood pressure must remain above 90 mmHg. ✓ Start using vasopressors, consider transferring to the intensive care unit (ICU), get echocardiography, and start various types of hemodynamic evaluation if hypotension remains despite two fluid boluses and anti-IL-6 medication. ✓ Dexamethasone 10 mg IV per six hours is an option.
	Hypoxia	✓ Additional oxygen ✓ Corticosteroids, supportive treatment, and tocilizumab or ✓ siltuximab, as prescribed for the control of hypotension
	Organ toxicity	✓ Symptomatic therapy of organ toxicities in accordance with accepted practices ✓ Corticosteroids and supportive treatment, as needed for hypotension; tocilizumab or siltuximab
Grade 3	Hypotension	✓ As required, IV fluid boluses, as advised for grade 2 CRS ✓ Vasopressors as required ✓ Tocilizumab and siltuximab, as advised for grade 2 CRS, if not already prescribed ✓ Transfer to ICU, do echocardiography, and evaluate the blood pressure as required for grade 2 CRS. ✓ Handle the fever and constitutional discomfort as suggested for grade 1 CRS; Dexamethasone 10 mg IV per 6 hours; if resistant, escalate to 20 mg IV per 6 hours.

Grade	Manifestation	Recommendations
	Hypoxia	✓ Tocilizumab or siltuximab combined with corticosteroids along with supportive treatment, as previously mentioned ✓ High-flow and non-invasive oxygen supply
	Organ toxicity	✓ Symptomatic therapy of organ toxicities in accordance with accepted practices ✓ The previously mentioned combination of tocilizumab or siltuiximab with corticosteroids, along with supportive care
Grade 4	Hypotension	✓ As specified for the care of grade 3 CRS, IV fluids, anti-IL-6 medication, vasopressors, and hemodynamic evaluation ✓ 1 g per day IV methylprednisolone ✓ · Treat the fever and any constitutional manifestations as you would grade 1 CRS
	Hypoxia	✓ Mechanical ventilating ✓ The previously mentioned combination of tocilizumab or siltuximab with corticosteroids, along with supportive treatment
	Organ toxicity	✓ Symptomatic therapy of organ toxicities in accordance with accepted practices ✓ The previously mentioned combination of tocilizumab or siltuximab with corticosteroids, along with supportive therapy

Table 2. CRS management strategy based on grades

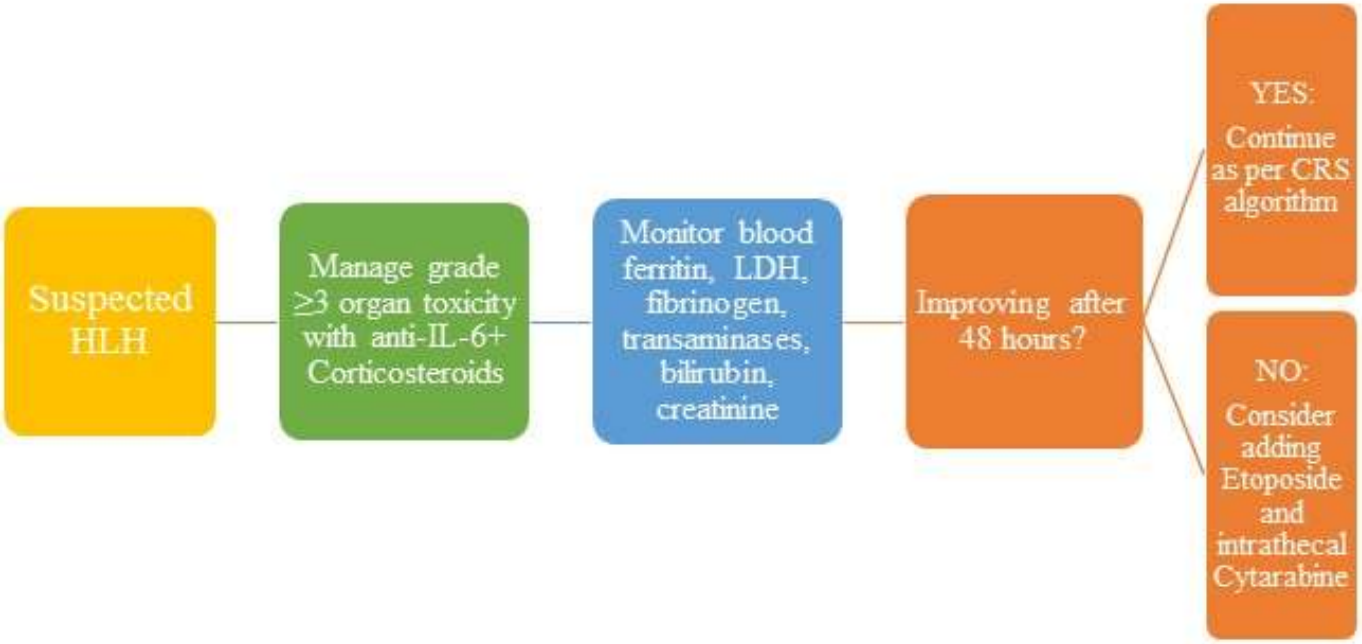

Figure 1. Instructions for treating HLH/MAS caused by CAR T cells

Seizure

None of the patients who received CAR-T cell therapy had ever had seizures before. However, seizures developed in 1% to 32% of them (9, 30, 32). In some circumstances, seizures with signs of a localized origin are just generalized tonic-clonic seizures (22, 30). Up to 10% of patients getting therapy for acute seizures eventually developed epilepsy (32, 33). Although MRI, transcranial Doppler ultrasound imaging, CT, and CT angiography all revealed no evidence of acute disease, EEG revealed generalized encephalopathy-like slowing (9, 32). Patients who have partial seizures usually react to corticosteroids, a second-line antiepileptic drug, and benzodiazepines (33, 34). All patients experiencing seizures after CAR-T cell treatment must be sent to the ICU, as these patients are in danger of rapidly worsening and proceeding to status epilepticus and, in rare instances, cerebral edema (33, 35, 36). Seizures may remain longer despite the quick use of seizure rescue medicines (32).

Cardiovascular Toxicities

There are presently no clear standards for CAR T-cell recipients' risk classification for early identification and therapy of cardiovascular toxicity. We propose employing an initial ECG, chemical panel, and transthoracic echocardiography to screen for cardiovascular comorbidities prior to treatment based on the information at hand. Patients above the age of 60, those with established left ventricle insufficiency, or those with at least two high-risk concurrent diseases may be considered high-risk (37). Before CAR T-cell therapy, patients who meet the aforementioned criteria and are extremely susceptible to cardiovascular toxicity should be sent to a cardio-oncologist for an assessment of their heart health. A comprehensive risk evaluation by a cardio-oncologist can assist in creating individualized clinical treatment

plans in anticipating a potential cardiovascular complication for a higher-risk patient, despite the fact that due to the typically invasive nature of cancer, which calls for CAR T-cell therapy, there may not be much time for optimizing drugs. Patients who experience high-grade CRS (grade 2) after receiving CAR T cells should be monitored closely for cardiac toxicities such as new or worsened arrhythmias or heart failure. With the help of further cardiac biomarkers, an ECG, or echocardiography, these patients need to be under close observation. In the end, these patients should additionally visit a cardio-oncologist following any complication for careful monitoring and additional management (4).

Guideline-directed medical therapy (GDMT) or anti-arrhythmic treatment must be used in patients with signs of cardiotoxicity in addition to aforementioned drugs, if clinically required. As of right now, tocilizumab, an IL-6 inhibitor, is the first-line therapy for severe CRS. Corticosteroids are typically only used for CRS that is resistant, and as the situation gets better, they are quickly reduced. Although new results indicate that high-dose corticosteroids may not have an influence on CAR T-cell effectiveness, this is mostly owing to worries about the possible unfavorable outcomes of corticosteroids on CAR T-cell efficacy (24, 38). However, no study has been conducted on how tocilizumab, corticosteroids, or preventive GDMT can influence CAR T-cell-induced cardiac toxicities (4).

CAR-T-Cell-Related Encephalopathy Syndrome

Another typical side effect of CAR-T cell therapy is CRES, which is often referred to as CAR-T cell-related neurotoxicity. It typically happens at the same time as CRS or after CRS. Headache, wooziness, confusion, epilepsy, and cerebral edema are among the symptoms of CRES. The fundamental pathogenic mechanisms of CRES are poorly known because there are no adequate animal models. High tumor burden, excess CAR-T cell growth, and severe CRS may all be linked to a higher chance of developing CRES. At present, a recognized pathway contributing to the development of CRES is immune-mediated endothelial activation (30, 39, 40). When CAR-T cells recognize target antigens, they quickly multiply and release cytokines that stimulate intrinsic immune cells like macrophages. These cells then stimulate cerebral endothelial cells, which ultimately leads to tight junctions becoming damaged and increases BBB permeability (30, 40). The increased blood cytokine levels then passively diffuse into the BBB, and the enhanced pro-inflammatory cytokine amounts in CSF appear to be related to CRES (41, 42, 43). Additionally, it has been shown that the breakdown of the BBB allows T cells, macrophages, and CAR-T cells to enter the CNS (22, 43, 44, 45). These engulfed immune cells and cytokines may cause the microglia to become activated, intensifying the regional inflammation reaction and ultimately leading to neurotoxicity (22, 30, 46, 47, 48). Consequently, immune-mediated endothelium damage is a factor that initiates CRES (30, 39, 40, 49). Tocilizumab's effectiveness in the treatment of CRES is restricted because it couldn't penetrate the BBB. It is advised for the management of CRES, considering the greater CNS permeability of corticosteroids (24).

CRS-related Coagulopathy

Coagulation disorder is usually noticed within one month of CAR-T cell infusion and is a newly recognized toxicity (50, 51). It is also referred to as CRS-related coagulopathy because of the positive link between its severity and the CRS grade and IL-6 levels (52). According to recent studies, half of patients receiving CAR-T therapy experience coagulopathy (50, 52, 53). Patients with coagulation disorder exhibit a wide range of aberrant coagulation variables, which are primarily indicated by raised D-dimer levels, diminished fibrinogen amounts, and delayed prothrombin times. Three phases of CRS-related coagulopathy's progression could be distinguished: the hypercoagulable phase, the consumptive hypo-coagulable phase, as well as the hyperfibrinolysis phase (52). The prompt and efficient care of CRS may assist in lowering the occurrence of coagulopathy because cytokine storm is a key factor in CRS-related coagulopathy. Without prompt and successful care, some patients with coagulopathy may continue to develop DIC, which comes with an unfavorable outcome (50, 52, 54).

Hemophagocytic Lymphohistiocytosis (HLH)/ Macrophage Activation Syndrome (MAS)

A collection of extremely severe immune illnesses known as HLH/MAS include hyperactive macrophages and lymphocytes, the generation of pro-inflammatory cytokines, lymphohistiocytic tissue invasion, and immune-mediated failure of multiple organs (55, 56). Regardless of the primary trigger, these illnesses have comparable clinical symptoms and are seen in approximately 1% of patients receiving CAR-T cell therapy. Clinical characteristics of patients with CRS mimic those of HLH/MAS. These include an elevated temperature, multiple organ failure, CNS events, elevated blood levels of ferritin, lactate dehydrogenase, soluble CD25, and cytokines, as well as decreased concentrations of fibrinogen (21, 55, 56, 57, 58). Therefore, HLH/MAS and CRS may be part of the same category of systemic hyperinflammatory illnesses. When left untreated, fulminant HLH/MAS is linked to significant mortality, whereas individuals with CRS typically respond to supportive therapy, anti-IL-6 treatments, and corticosteroid (59, 60). In the setting of CRS, the confirmation of HLH/MAS could be challenging. Numerous conventional diagnostic indicators for HLH/MAS, such as fever, splenomegaly, high levels of soluble CD25, and low or absent NK-cell activity, are not specific. Indeed, in the absence of CAR-T cell therapy, these characteristics are typically evident in individuals with even low-grade CRS as well as those with advanced-stage hemophilia (61). Therefore, new diagnostic standards are required for the detection of HLH/MAS in CRS patients treated with CAR-T cells.

It is recommended that a patient be diagnosed with CAR-T cell-related HLH/MAS if they experienced maximum ferritin levels of >10,000 ng per ml while on the CRS phase and a pair of the subsequent symptoms: grade 3 organ toxicities affecting the lung, kidney, or liver, or hemophagocytosis in the bone marrow or any other organs. According to the CRS guidelines, patients with probable HLH/MAS should be treated with anti-IL-6 treatment and corticosteroids for grade 3 organ toxicities. It has been shown that HLH/MAS that develops in a patient following receiving blinatumomab can be reversed with cytokine-directed treatment (62). The available information in settings besides CAR-T-cell treatment suggests that this medication is the preferable treatment for resistant HLH, so further treatment with etoposide 75-100 mg/m2 must be taken into consideration if the patient doesn't show signs of improvement clinically or serologically within 48 hours. Additionally, people with kidney and liver problems might utilize this medication (55, 59, 63). For individuals with a high likelihood of receiving a diagnosis of HLH, it is crucial to start etoposide prescription as soon as possible despite organ dysfunction because of the high risk of death (59, 60, 61). If necessary, etoposide might be administered again after 4–7 days based on clinical or serological indications for successful management of the disease. For individuals with HLH-related neurotoxicity, intrathecal cytarabine, either with or without hydrocortisone, must also be taken into consideration, even though etoposide and cytarabine are frequently utilized for treating hereditary and cancer-related HLH (55, 59, 63) (Figure 1). There is currently a lack of direct data to back up their usage in patients with CAR-T cell-associated HLH.

Although current therapies do not directly target these sorts of cells, the general aim of therapy for HLH is to inhibit the excessively active CD8+ T cells and macrophages that coordinate this immunological disease. In the foreseeable future, it is likely that medications under research for therapeutic use may be able to target particular cytokines that are essential to HLH/MAS, such as IFNγ. For instance, a humanized anti-IFNγ mAb, NI-0501, showed good tolerability and elicited responses in nine out of thirteen children with refractory primary HLH (69%)(6).

Future Perspectives

There are numerous obstacles that CAR-immune cell treatments must overcome, and investigation is now being done to find creative solutions. Because of their distinctive qualities, mesenchymal stem cells (MSCs) are advantageous for utilization. Clinicaltrials.gov does not presently show any clinical trials employing MSC in CAR-related immunotherapy. Nevertheless, numerous articles on preclinical research have demonstrated how MSC and CAR work together effectively in immunotherapy. This is a relatively novel therapeutic strategy that combines two distinct cellular immunotherapy treatments. Only a few experimental trials using MSC-assisted CAR-T cell immunotherapy or modified MSCs that express CAR exist at the moment (64).

Immunotherapies using CAR, however, have benefits as well as drawbacks. Utilizing MSC can help to get beyond these restrictions, including trafficking, immunosuppressive environments, and short-lived persistence. The versatile

potential of MSC, from delivering different anti-tumor agents like oncolytic viruses and tumor-specific prodrugs to presenting immunomodulatory proteins like chemokines and interleukins, not only improves the efficacy and safety of CAR-related immunotherapy but also offers a bright outlook for solid tumor treatment. It is worth mentioning that the benefits of using MSCs in the treatment of many diseases, including Covid-19 (65), Glioma (66), SLE (67), Stroke (68), Alzheimer's (69), Parkinson's (70), and other neurological and non-neurological disorders have been proven. In order to maximize the combined advantages of both CAR and MSC, it would be wise to either adapt MSCs to express CARs as a targeted therapy or use MSCs as a supplemental approach to deliver molecules and aid in CAR-based immunotherapies. Additionally, key preliminary perspectives into the possible application of MSC in CAR-T/NK cell immunotherapy would be provided by the impacts and mechanism of MSC in adoptive T/NK cell therapy (64).

Conclusion

Despite the fact that CAR T-cell therapy involves a number of serious side effects, it has been shown to be clinically significantly beneficial for a large number of patients. We now have continuing experience with CAR T-cell therapy, and this experience is the foundation for our recommendations for how to grade and handle adverse events. These recommendations will continue to change as our experience grows. As part of this progression, work is ongoing to improve and standardize the evaluation and management of CRS and neurologic episodes, which could assist in addressing some of the existing difficulties. The adoption of this potentially therapeutic technique will face fewer obstacles as we progress toward broad access outside of specialist centers thanks to better knowledge regarding probable adverse effects and their management.

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