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REVIEW

Side-effect management of chimeric antigen receptor (CAR) T-cell therapy

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Chimeric antigen receptor (CAR) T cells directed against the B-cell marker CD19 are currently changing the landscape for treatment of patients with refractory and/or relapsed B-cell malignancies. Due to the nature of CAR T cells as living drugs, they display a unique toxicity profile. As CAR T-cell therapy is extending towards other diseases and being more broadly employed in hematology and oncology, optimal management strategies of side-effects associated with CAR T-cell therapy are of high relevance. Cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and cytopenias constitute challenges in the treatment of patients with CAR T cells. This review summarizes the current understanding of CAR T-cell toxicity and its management.

Key words: Chimeric antigen receptor (CAR) T cells, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), CAR T-cell associated side-effects, CAR T-cell side-effect management

INTRODUCTION

Chimeric antigen receptor (CAR) T cells combine the antigen-binding properties of antibodies with the effector functions of T cells and have demonstrated unprecedented clinical responses when directed against CD19 in a variety of malignancies including pediatric[1,2] and adult[3,4] acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL)[5,6] and chronic lymphocytic leukemia (CLL).[7-10] Commercially manufactured second-generation CD19-directed CAR T cells, i.e. tisagenlecleucel (tisa-cel)[11] and axicabtagene ciloleucel (axi-cel),[12] have been approved for treatment of patients with relapsed and refractory (r/r) B-cell malignancies based on the pivotal trials ELIANA (ALL)[1] and JULIET [diffuse large B-cell lymphoma (DLBCL)][13] for tisa-cel and ZUMA-1 [DLBCL and primary mediastinal B-cell lymphoma (PMBCL)][14,15] for axi-cel. Both products have been adopted as standard of care within the labeled indications.[16-20] Recently, brexucabtagene autoleucel (brexu-cel) was approved for treatment of r/r mantle cell lymphoma (MCL).[5,21]

As cellular products, CAR T cells are associated with unique toxicities. Recognition, management and differentiation of CAR T-cell toxicities are crucial for safe and broad employment of this therapy. This review aims to summarize the clinical presentation, grading and management of the most relevant adverse effects associated with CAR T-cell therapy. For practical reasons, it will be largely restricted to those CAR T-cell constructs that are commercially available to date, i.e. CD19 CAR T cells for r/r ALL and NHL.

Cytokine release syndrome

Incidence, pathophysiology, clinical and laboratory characteristics of cytokine release syndrome. Cytokine release syndrome (CRS) is observed in the majority of patients with ALL[1,2] and lymphoma[5,14,22] treated with CD19 CAR T cells, but also with CAR T cells targeting B-cell maturation antigen (BCMA),[23,24] CD22,[25] CD123,[26] and other T cell engaging therapies.[27,28]

As a supraphysiologic inflammatory state, CRS (Figure 1) is triggered by inflammatory cytokines and chemokines released by CAR T cells, e.g. interferon (IFN) γ, tumor necrosis factor (TNF) α, granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-2, IL-8 and IL-10, after engaging with the corresponding target antigen.[29,30] This activates bystander host antigen-presenting cells (APCs) as well as further T cells.[14,29,31-34] Xenogeneic models emphasize the role of host immune cells in the pathogenesis of CRS demonstrating that not CAR T cells but monocytes, macrophages and dendritic cells are the primary source of IL-6, a key player in CRS,[29,35,36] and IL-1.[36,37] Depletion of macrophages[38] and elimination of monocytes[36] reduce the severity of CRS. Also, inhibition of GM-CSF signaling can decrease CRS symptoms.[30,39] Other inflammatory cytokines and chemokines involved in CRS include IL-15, CRP, ferritin, macrophage inflammatory protein 1α (MIP1α) (CCL3), MIP1ß (CCL4), monocyte

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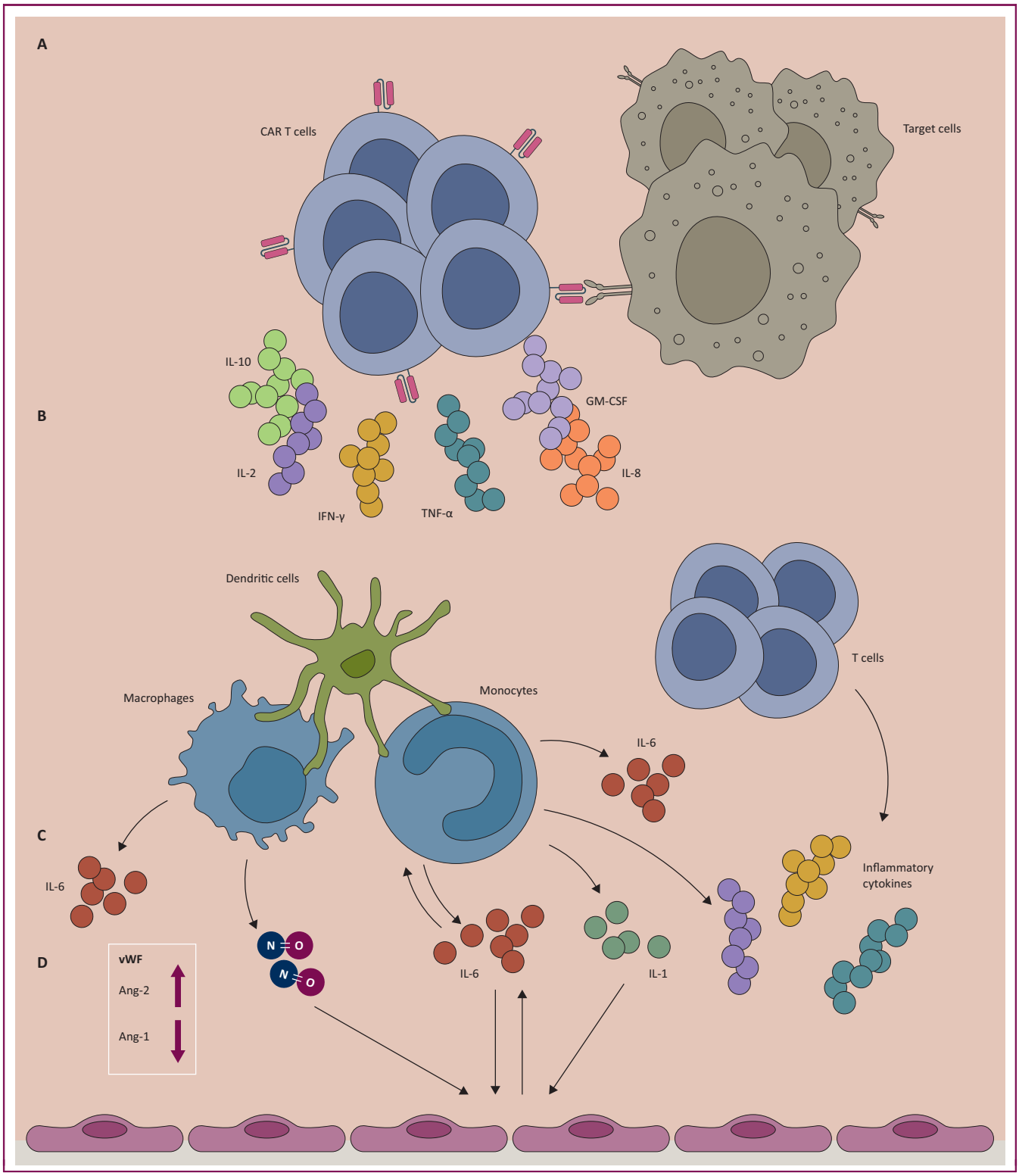

Figure 1. Potential pathophysiology of CAR T-cell mediated cytokine release syndrome (CRS).
Inflammatory cytokines, e.g. tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-2, IL-8, IL-10 and granulocyte macrophage colony-stimulating factor (GM-CSF) are produced by CAR T cells that are activated following engagement with corresponding target cells as well as by direct target cell lysis (A). This initial inflammatory response recruits and activates bystander immune cells, e.g. monocytes, macrophages and dendritic cells (DC) and other T cells (B), which potentiate the immune response by releasing IL-1 and IL-6 as well as nitric oxide (NO) (C). Hyperinflammation activates the endothelium, which further releases IL-6, resulting in a positive CRS feedback loop, and endothelial permeability factors such as von Willebrand factor (vWF) and angiopoietin (Ang)-2 (D). This destabilizes vascular integrity in CRS patients and mediates hemodynamic instability, capillary leak and consumptive coagulopathy.

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chemoattractant protein-1 (MCP-1; CCL2) and soluble IL-2 receptor α (sIL2Rα).[32,33,40,41] Hyperinflammation activates the vascular endothelium, which further releases IL-6 resulting in a positive CRS feedback loop.[42] Elevated levels of endothelial permeability factors such as von Willebrand factor (vWF) and angiopoietin (Ang)-2 as well as decreased levels of the endothelium stabilizer Ang-1 account for loss of vascular integrity, hemodynamic instability, capillary leak and consumptive coagulopathy in CRS.[32,43,44] Nitric oxide generated by the macrophage-derived nitric oxide synthase can further potentiate vasodilatation and hemodynamic instability in CRS.[35]

CRS manifests with constitutional symptoms such as fever associated with fatigue, myalgia, arthralgia, rigors or anorexia, but can rapidly progress to hypotension, tachycardia, tachypnea and hypoxia, arrhythmia, capillary leak, coagulopathy, respiratory failure, shock and organ dysfunction.[45-47] The risk of developing CRS depends on a variety of disease-, procedure-, and product-related factors summarized in Table 1.

Median time to onset of CRS varies depending on the specific CAR T-cell product used and the targeted disease. For tisa-cel comprising a 4-1BB (CD137) costimulatory domain, the CRS risk peaks at 3 and 7 days after CAR T-cell administration for ALL and DLBCL patients, respectively,[1,13] whereas onset of CRS symptoms in patients treated with axi-cel or brexu-cel, containing CD28 as costimulatory domain, is earlier, usually 2 days after CAR T-cell administration.[5,14,40] Nonetheless, delayed CRS occurring up to 3 weeks after CAR T-cell administration has also been reported.[31,32,48]

CRP and ferritin have been proposed as biomarkers for CRS prediction, as they correlate with the severity of CRS.[3,7,33] However, CRP does not always precede CRS and hence has a low positive predictive value.[33,40] Instead, elevation of MCP-1 combined with fever $\geq$38.9°C within 36 h of CAR T-cell administration has demonstrated higher sensitivity and specificity predicting high-grade CRS.[32] Altogether, in the absence of established pre-emptive interventions, biomarker monitoring for CRS has not gained practical importance yet.

Grading of CRS. The severity of CAR T-cell-induced CRS has been assessed using different grading systems.[1,3,13,31,49,50] This resulted not only in differences in reported CRS incidences of clinical trials but has also significantly hampered comparability of safety profiles of different CAR T-cell products.

In an attempt to standardize CRS grading and toxicity management, the CAR T-cell Therapy-Associated Toxicity (CARTOX) Working Group established a multi-institutional scoring system in 2018.[40] CARTOX CRS grading is based on three vital signs (temperature, blood pressure (RR) and oxygen saturation) as well as organ toxicity assessed according to the Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 of the National Cancer Institute.[49] Eventually, in 2019, consensus guidelines that further simplified CRS grading were defined by the American Society for Transplantation and Cellular Therapy (ASTCT).[51] According to these guidelines, fever (defined as temperature $\geq$38°C) that is temporally associated with CAR T-cell administration (within 24 h to 3 weeks)[47] is the prerequisite for CRS diagnosis. Hypotension (defined as systolic, diastolic or mean arterial RR below patient's baseline) and hypoxia (oxygen required to overcome a perceived deficit in oxygenation) are the principal determinants of CRS grade and severity (Table 2). Organ toxicities no longer contribute to CRS grading. Retrospective comparison of the different grading systems has demonstrated that ASTCT grading allows for objective, reproducible, accurate, easy-to-use and rapid assessment of CRS severity in patients based on clinical signs and symptoms.[52,53] It is anticipated that ASTCT grading will be universally adopted to report toxicities in both clinical trials and routine care.

Management of CRS. Although consensus guidelines are standardizing CRS grading assessment, evidence-based guidelines for CRS management are pending. Nonetheless, as experience with CAR T cells is expanding, management principles are being continuously refined. The current status is summarized in Table 2, although treatment decisions should be made at the bedside according to the respective clinical situation of the patient.

For 'grade 1 CRS' comprising fever and non-specific constitutional symptoms without hypotension or hypoxia, management is primarily supportive, i.e. with antipyretics and fluids. CRS-mediated fever is a diagnosis of exclusion[54] and a symptom-oriented diagnostic infection work-up including blood cultures, laboratory tests and appropriate imaging should be carried out and empiric antibiotic treatment as per institutional guidelines initiated.

If, in addition to fever, mild hypotension not requiring vasopressors and/or hypoxia that can be resolved with low-flow oxygen ($\leq$6 l/min) occurs, 'grade 2 CRS' is diagnosed according to the ASTCT guidelines. Here, hypotension should be treated with intravenous (IV) hydration (20 ml/kg up to 1 l) and hypoxia with supplemental low-flow oxygen via nasal cannula. Concerning hydration, fluid replacement should be monitored cautiously given the risk of vasodilatation, capillary leak and consequent edema in patients with progressive CRS. Whereas crystalloids are commonly used for critically ill patients, albumin solutions have been suggested as superior for CRS patients by reducing the risk

Table 1. Risk factors associated with CRS in CD19-directed CAR T-cell therapy

Risk factors for CRS
High disease burden[4,32,60,140,173]
ALL as underlying disease[174]
High number of administered CAR T cells[2,32,90,141,174,175]
High peak of CAR T-cell expansion[32,60,141,173]
Thrombocytopenia and endothelial activation before CAR T-cell treatment[32]
Lymphodepleting therapy with fludarabine and cyclophosphamide[32,90,175]
CD28 costimulatory domain[176]

ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome.

Table 2. Grading and proposed management of cytokine release syndrome (CRS) adapted from ASTCT CRS grading consensus guidelines by Lee et al.[51] and Neelapu[53]

Grade	Fever	Hypotension[a]	Hypoxia[a]	Management
1	Temperature ≥38.0°C	—	—	**Supportive management** Antipyretics, IV hydration infectious diagnostic work-up; initiate anti-infective treatment
2		No vasopressor required	Low-flow O_2 (≤6 l/min; nasal canula)	**Continue supportive management of CRS grade 1** IV fluid boluses Supplemental oxygen Tocilizumab (8 mg/kg BW/dose in patients ≥30 kg BW; 12 mg/kg BW in patients <30 kg BW; IV administration; maximum of 800 mg/dose) ± corticosteroids (dexamethasone 10 mg every 6-8 h or methylprednisolone equivalent)
3		1 vasopressor	High-flow O_2 (≥6 l/min; high-flow nasal canula, mask, NIV)	**Continue supportive management of CRS grade 1** Consider ICU management Vasopressor support and/or supplemental O_2 Tocilizumab (8 mg/kg BW/dose in patients ≥30 kg BW; 12 mg/kg BW in patients <30 kg BW; IV administration; maximum of 800 mg/dose) + dexamethasone 10-20 mg IV every 6 h or methylprednisolone equivalent
4		>1 vasopressor	Positive pressure (CPAP, BiPAP, mechanical ventilation)	**Continue supportive management of CRS grade 1** ICU management Vasopressor support and/or supplemental O_2 via positive pressure Tocilizumab (8 mg/kg BW/dose in patients ≥30 kg BW; 12 mg/kg BW in patients <30 kg BW; IV administration; maximum of 800 mg/dose) + methylprednisolone 1000 mg/day

BiPAP, bilevel positive airway pressure; BW, body weight; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; ICU, intensive care unit; IV, intravenous; NIV, non-invasive ventilation; O_2, oxygen; PAP, positive airway pressure.
[a] Below patient's baseline.

of capillary leak and pulmonary edema as well as ameliorating endothelial dysfunction.[55-57]

Abrogation of IL-6 using the monoclonal antibody tocilizumab can be considered in patients with CRS grade 2, even though the optimal timing of anti-cytokine treatment has not yet been established.

Early use of tocilizumab can reduce the rate of severe CRS and end-organ dysfunctions without affecting expansion, persistence and response rates of CAR T cells and[1,4,14,37,45,58] prophylactic use of tocilizumab in CAR T-cell patients or administration in patients with fever alone has been evaluated.[58,59] However, other trials suggest that tocilizumab may be associated with ablation of the cytokine milieu necessary for CAR T-cell proliferation and CAR T-cell activity,[47] and an increased risk of neurotoxicity[40,59] by increasing the levels of peripheral IL-6 that can cross the blood-brain barrier (BBB).[29,60-64] ASTCT consensus recommends tocilizumab for CRS ≥grade 2 (8 mg/kg body weight (BW)/dose in patients ≥30 kg BW; IV administration over 1 h; 12 mg/kg BW in patients <30 kg BW; maximum of 800 mg/dose; administration up to four doses with 4 to 6 h between consecutive doses).[65] Preemptive use of tocilizumab has not been addressed in current CRS management algorithms and is therefore not recommended.[51,53,66]

Tocilizumab exerts anti-CRS effects by inhibition of the IL-6 receptor. IL-6 can act via three signaling mechanisms: classic cis and *trans*-signaling as well as *trans*-presentation. In classic *cis*-signaling the cytokine binds to the membrane-bound IL-6 receptor expressed on macrophages, hepatocytes, neutrophils and T cells. Binding induces dimerization of the glycoprotein 130 (gp130) and activates the Janus kinase/signal transducer and activation of transcription (JAK/STAT) pathway.[67] In *trans*-signaling, IL-6 binds to the soluble IL-6 receptor and this complex associates with gp130 to activate intracellular signaling.[68] In *trans*-presentation, IL-6 is presented via membrane-bound IL-6 receptors on immune cells to receptors on T cells, which results in gp130 engagement.[69,70]

Tocilizumab blocks membrane-bound as well as soluble IL-6 receptors and can therefore suppress all three mechanisms of IL-6 signaling.[71] Tocilizumab was approved for CRS treatment based on retrospective data demonstrating improvement of patients with severe CRS after CD19-directed CAR T-cell treatment 4-5 days after tocilizumab administration.[72] Besides an increased risk of cytopenia and infection in patients with rheumatoid arthritis,[73] tocilizumab has a favorable side-effect profile[72] and has become the standard-of-care therapy for moderate to severe CRS. Of note, inhibition of IL-6 signaling results in rapid decrease of CRP.[40]

For patients with clinical deterioration despite at least two doses of tocilizumab as well as for patients with increased risk of severe CRS and neurotoxicity, additional treatment with corticosteroids should be considered.[47,53,74] In contrast to tocilizumab, corticosteroids exert non-specific anti-inflammatory effects that abrogate inflammation by inhibiting CAR T cells as well as bystander immune cells.[75] Although initial studies reported reduced expansion and lacking persistence of CAR T cells in patients who received corticosteroids,[3] early steroid use in subsequent studies has

not been associated with detrimental effects on clinical remission rates or CAR T cell persistence.[76,77] With regards to the choice of the corticosteroid agent, dexamethasone at a dosage of 10 mg every 6-8 h or methylprednisolone at a dose of 1-2 mg/kg BW are most commonly used,[78] with dexamethasone being preferred in case of concomitant neurotoxicity due to superior central nervous system (CNS) penetration and improvement of the integrity of the BBB.[79-82] After resolution of hypotension and hypoxia, tapering of corticosteroids should be carried out based on the patient's individual response.[83]

For patients with 'grade 3 CRS', i.e. patients with fever and hypotension not responding to fluids and/or with high-flow oxygen requirement (≥6 l/min), intensive care unit (ICU) management should be considered. Patients should receive tocilizumab and corticosteroids, i.e. dexamethasone 10-20 mg or its equivalent of methylprednisolone.[51,53,74] To prevent further deterioration and end-organ damage, vasopressors and/or high-flow oxygen (via nasal cannula, face mask, or Venturi mask)[51,53,74] are advised. Regarding vasopressors, norepinephrine has been most widely used as first-line adrenergic agonist for hemodynamic support in CRS patients.[78] However, catecholamine feedback loops may contribute to maintenance of CRS in affected patients,[84] raising the question of whether non-adrenergic vasopressors such as vasopressin might be more beneficial than adrenergic agonists in this setting. Due to common new-onset cardiac dysfunction in patients with high-grade CRS,[85,86] cardiac monitoring, including regular echocardiograms, is advised.

Requirement of multiple vasopressors and/or hypotension requiring positive pressure ventilation [continuous positive pressure airway (CPAP), bilevel positive airway pressure (BiPAP), intubation and mechanical ventilation] is considered 'grade 4 CRS'. Here, management as in grade 3 should be continued, with methylprednisolone 1000 mg/day being used as corticosteroid of choice.[51,53,74,87]

With early and aggressive management, even high-grade CRS is reversible.[74] As experience with CAR T cells and their related toxicities is growing, the rate of ICU admissions after CAR T-cell treatment compared with early CAR T-cell trials, in which approximately 45%-50% of patients required intensive care treatment,[14,88] has significantly decreased.[89] Of note, resolution of CRS can result in an anti-CRS syndrome with patients experiencing hypothermia and bradycardia[74] that has been associated with shifts in cytokine levels. Hence, monitoring of patients even after successful CRS treatment is advised.

Immune effector cell-associated neurotoxicity syndrome

Pathophysiology, clinical and laboratory characteristics of ICANS. Neurotoxicity is another common acute toxicity observed in up to 64%[14] of CAR T-cell clinical trials.[1,2,4,8,13,14,19,44,90,91] High-grade ICANS is likely more frequent for CAR-constructs comprising CD28 as costimulatory domain, where it can occur in up to 45% of treated patients.[4,14,15,19,92] In contrast, using 4-1BB-containing CAR T cells, i.e. tisa-cel, ICANS develops less frequently, with severe ICANS observed in up to 13% of patients.[1,22] Apart from CD19, neurotoxicity has also been observed with CAR T cells targeting CD22,[93] BCMA[23,24,94,95] and other hematopoietic antigens.[96,97] Moreover, similar neurotoxic symptoms have been reported with other immune effector cell (IEC) engaging therapies, e. g. blinatumomab[98] or haploidentical donor natural killer (NK) cells[99] and, therefore, neurotoxicity was renamed from CAR T-cell related encephalopathy syndrome (CRES)[40] to ICANS.[51]

ICANS can occur concomitantly with CRS, after resolution of CRS or independently of CRS.[31,74,88] In the latter case, neurological symptoms tend to be mild.[100] Usually, ICANS presents 4-5 days after CAR T-cell administration,[101] but delayed ICANS occurring 3-4 weeks after CAR T-cell treatment has also been reported.[40,43,44,102] ICANS typically presents with impairment of attention and confusion. Expressive aphasia[44] and changes in handwriting[40,74] are considered fairly specific and early signs of ICANS. ICANS can progress to depressed level of consciousness, coma, seizures, motor weakness and cerebral edema. Fatal neurotoxicity due to cerebral edema has been reported with an incidence of 3%[43] after CD19-directed CAR T-cell treatment with either CD28[19,103] or 4-1BB[43] constructs. All cases of fatal cerebral edema were associated with CRS,[43,100] and severe CRS has been shown to be associated with severe ICANS.[1,2,14,33,43,44,104] Apart from the risk factors associated with CRS, other risk factors for ICANS include elevated pre-treatment lactate dehydrogenase (LDH) and decreased platelet[41] or endothelial growth factor[44] levels, elevated serum Ang-2/Ang-1 ratio,[43] higher ferritin concentration on day 3 after CAR T-cell administration,[44] and pre-existing neurologic comorbidities[43] (Table 3).

Contrary to CRS, the pathophysiology of ICANS is less well understood. CNS trafficking of CAR T cells,[3,40,60,105] passive diffusion of cytokines, (e.g. IL-6 and IL-15) into the CNS,[43,44,106] endothelial activation with subsequent BBB disruption,[43,44] microglial[22,107] and/or myeloid cell activation in the CNS with secretion of IL-1 and IL-6,[35,36] and elevated levels of IL-15,[108] or N-methyl-D-aspartate (NMDA) receptor agonists (e.g. glutamate and quinolinic acid)[44] have all been suggested to contribute to ICANS (Figure 2).

Table 3. Risk factors associated with immune effector cell-associated neurotoxicity syndrome (ICANS) in CD19-directed CAR T-cell therapy

Risk factors for ICANS
CRS[2,43]
Pre-existing neurologic comorbidities[43,104]
High disease burden[19,43,44]
High number of administered CAR T cells[43] and high peak of CAR T-cell expansion[44]
ALL as underlying disease[43]
Elevated lactate dehydrogenase (LDH), thrombocytopenia and endothelial activation before CAR T-cell treatment[41,43]
Elevated ferritin concentration <72 h after CAR T-cell administration[44]
CAR-design: CD28 costimulatory domain,[100,176] certain hinge and transmembrane CAR domains[177]
Lymphodepleting therapy with fludarabine and cyclophosphamide[43]

ALL, acute lymphoblastic leukemia; CRS, cytokine release syndrome.

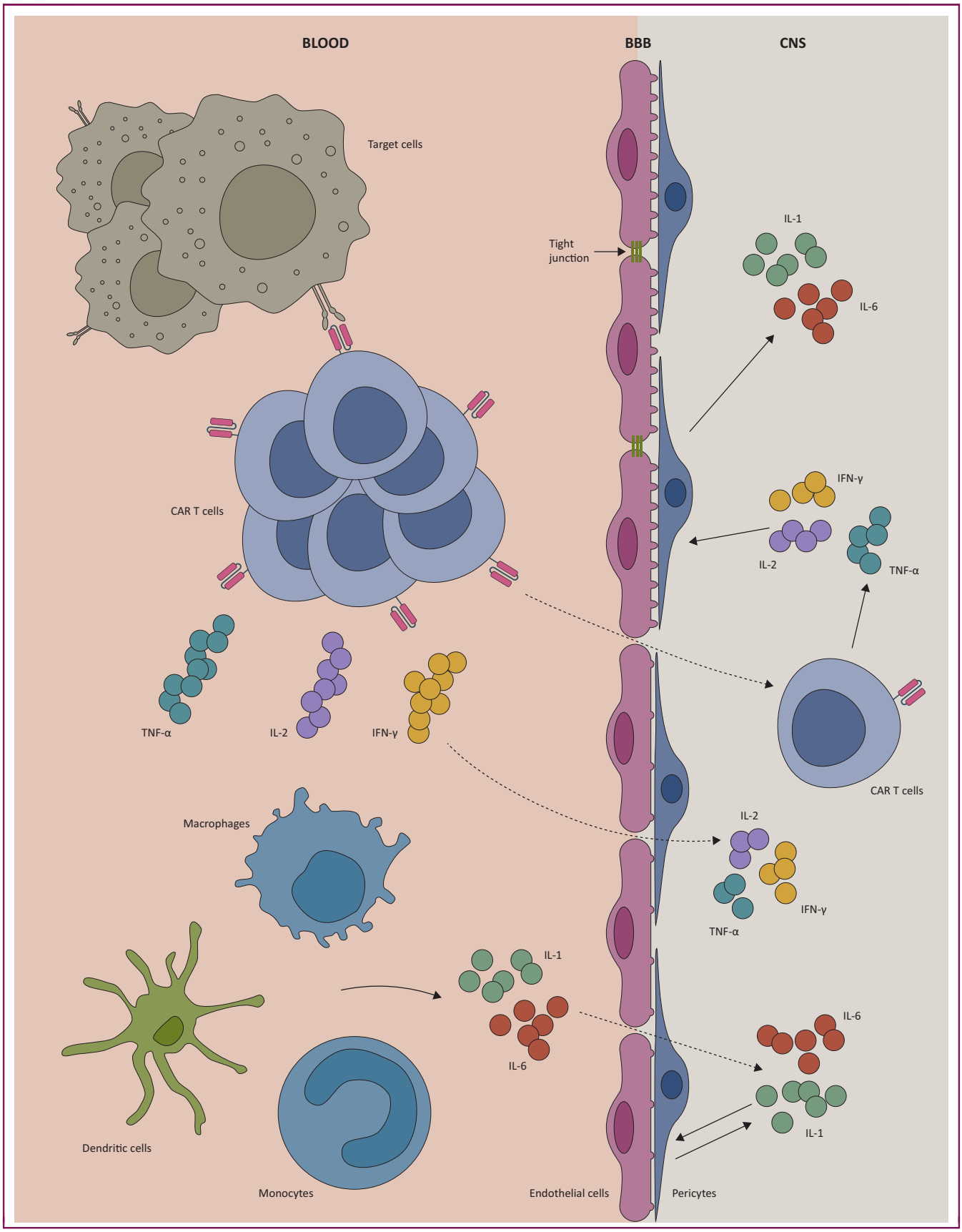

Figure 2. Potential pathophysiology of immune effector cell-associated neurotoxicity syndrome (ICANS).
The underlying pathophysiology of ICANS has not yet been fully understood, but endothelial activation with subsequent blood-brain barrier (BBB) disruption, trafficking of CAR T cells and passive diffusion of cytokines into the central nervous system (CNS) together with pericyte activation with subsequent cytokine production and astrocyte activation have been proposed to contribute to ICANS. DC, dendritic cell; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

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Grading of ICANS. CAR T-cell-associated neurotoxicity was graded initially according to CTCAE, but this had many shortcomings assessing CAR T-cell specific symptoms.[49] The CARTOX Working Group introduced the term CRES taking into account the unique profile of CAR T-cell associated neurotoxicity[40] and included a 10-point scale (CARTOX-10) adapted from the Mini-Mental State Examination[109] to evaluate cognitive skills (i.e. orientation to space, time and personality), and assessment of speech and writing abilities. Due to its practicality and objectivity, it represented a suitable screening tool for neurotoxicity in CAR T-cell patients. Besides the CARTOX-10, further parameters within the CRES grading system are the assessment of seizures, motor weakness, and signs of elevated intracranial pressure (ICP) evaluated via papilledema or cerebrospinal fluid opening pressure on lumbar puncture (LP).[40] However, ICP assessment is particularly difficult to implement in the clinic. Consequently, the ASTCT consensus guidelines implemented a modified version of the CARTOX grading system that combines an improved CARTOX-10 screening tool, the IEC-associated encephalopathy (ICE) score, with the evaluation of consciousness level (defined as the degree of stimulation required for a patient to respond), occurrence of seizures, motor findings and signs of elevated ICP (Table 4). Compared with the CARTOX-10 score, the ICE score (Table 5) includes assessment of receptive aphasia.[51] Non-specific neurologic symptoms such as headache, tremor, myoclonus, hallucinations, balance problems and intracranial hemorrhage were excluded from ICANS diagnosis[51] and are graded according to CTCAE. For pediatric patients, ICE is replaced by the Cornell Assessment of pediatric delirium scale,[110] whereas other ICANS criteria remain unchanged.[64] Recent retrospective comparison of CTCAE and ASTCT confirmed suitability and practicality of ASTCT ICANS grading.[111]

Management of ICANS. For isolated ICANS, steroids are the first-line therapy (Table 4). Tocilizumab has poor BBB penetration,[112] has shown limited efficacy in resolving neurologic toxicity[36,43,44,64,90] and been associated with increased risk and severity of neurotoxicity.[14] Therefore, it should only be administered in cases of ICANS with concurrent CRS.[14,31,40,108]

Similar to CRS, 'grade 1 ICANS' is primarily managed by supportive care and close monitoring. Other potential etiologies, such as stroke, malignancy, infection or hemorrhage, need to be excluded by appropriate diagnostic tests. The role of imaging is unclear given that it can be normal despite neurotoxicity,[43,60] but should be carried out nonetheless in all patients with signs of neurotoxicity

Table 4. Grading and proposed management of immune effector cell-associated neurotoxicity syndrome (ICANS): according to and adapted from ASTCT ICANS grading consensus guidelines by Lee et al.[51] and Neelapu[53]

Grade	ICE score	Consciousness	Seizure	Motor findings	Elevated ICP/edema	Management
1	7-9	Awakens spontaneously	—	—	—	**Supportive management** EEG Neuroimaging Lumbar puncture Tocilizumab only if concurrent CRS
2	3-6	Awakens to voice	—	—	—	**Continue supportive management of ICANS grade 1** Consider dexamethasone 10 mg ever 6-8 h or methylprednisolone equivalent
3	0-2	Awakens only to tactile stimulus	Any seizure that resolves rapidly ± intervention	—	Focal or local edema on imaging	**Continue supportive management of ICANS grade 1** ICU treatment recommended Dexamethasone 10-20 mg IV every 6 h or methylprednisolone equivalent Control seizures with anti-epileptics Treat focal/local edema with methylprednisolone 1000 mg/day Consider airway protection
4	0[a]	Vigorous stimuli required, unarousable, stupor, coma	Prolonged life-threatening seizure (>5 min) or repetitive seizure without return to baseline	Deep focal weakness, i.e. hemiparesis, paraparesis	Diffuse cerebral edema on imaging or papilledema or decerebrate/decorticate posture or cranial nerve VI palsy or Cushing's triad (bradycardia, hypertension and abnormal breathing)	**Continue supportive management of ICANS grade 1** ICU treatment High-dose methylprednisolone 1000 mg/day Airway protection, e.g. by intubation and mechanical ventilation Control seizures with anti-epileptics Lower elevated ICP with hyperventilation, hyperosmolar therapy or neurosurgery

CRS, cytokine release syndrome; EEG, electroencephalography; ICE, immune effector cell-associated encephalopathy; ICP, intracranial pressure; ICU, intensive care unit.
[a] ICE score 0 classified as ICANS grade 3 if patient is awake with aphasia; grade 4 if patient is unarousable and unable to perform ICE assessment.

Table 5. Immune effector cell-associated encephalopathy (ICE) assessment adapted from ASTCT grading consensus guidelines by Lee et al.[51]

ICE parameter	Task	Scoring points
Orientation	Orientation to year, month, city, hospital	4 × 1
Naming	Ability to name three objects	3 × 1
Follow command	Ability to follow simple tasks	1
Writing	Ability to write a standard sentence	1
Attention	Ability to count backwards from 100 by 10s	1

to exclude alternative diagnoses and incipient edema, and to monitor the evolution of prior abnormalities. Electroencephalography most commonly shows diffuse slowing, a non-specific indicator of encephalopathy that is frequently detected in critically ill patients,[40,43,44] but is a suitable tool to detect subclinical seizures in ICANS. Because neurotoxicity is frequently associated with signs of increased trafficking of cells and proteins across the BBB, LP will often demonstrate elevated protein concentration and lymphocyte counts, including CAR T cells, in the cerebrospinal fluid.[43,44,106]

Corticosteroids should be considered for 'grade 2 ICANS' and are indicated for 'grade 3 ICANS'. Dosing of corticosteroids can vary based on the neurologic symptoms, but usually dexamethasone 10 mg IV every 6-8 h is administered. For 'grade 4 ICANS', methylprednisolone 1000 mg IV for 3 days has been recommended. So far, short-course steroids (<10 days) have been shown not to affect response or progression-free survival.[41] High-grade ICANS should be treated in an ICU and include potential airway protection by mechanical intubation.[40,87] Apart from high-dose corticosteroid treatment, in patients experiencing signs of cerebral edema, elevation of the head, hyperosmolar therapy with mannitol or hypertonic saline and hyperventilation are advised.[40,113]

Although seizures can occur in ICANS, the role of anti-epileptic prophylaxis has not yet been determined. Distinct approaches, including prophylaxis for all patients,[40] prophylaxis of patients with CRS[106,114] or no prophylaxis until development of neurologic symptoms[40] have been advocated. Levetiracetam, due to its favorable side-effect profile and limited drug interaction, is the agent of choice for prophylaxis.[40,115] Given that seizures have been observed despite levetiracetam,[43,44,106] primary seizure prophylaxis is currently not routinely recommended. Nonetheless, it is advised for patients with a history of seizures or CNS disease.[87,116,117] For active seizures, benzodiazepines and additional anti-epileptics (levetiracetam or phenobarbital) are considered the treatment of choice.[14,40,53,113]

Similar to CRS, ICANS can be reversible in most patients,[41,104,118] although resolution of neurologic symptoms usually takes longer than in CRS.[117]

CRS and ICANS refractory to tocilizumab and/or corticosteroids

If patients with CRS and/or ICANS continue to deteriorate despite aggressive supportive treatment and the use of tocilizumab and corticosteroids, alternative third-line anti-cytokine treatment can be considered. Siltuximab is a monoclonal antibody that binds IL-6 rather than the IL-6 receptor. Contrary to tocilizumab, siltuximab might have the benefit of preventing ICANS by removing IL-6 from the circulation. Siltuximab has been used at doses of 11 mg/kg BW/dose for the treatment of CRS.[19,40,47,61]

Anakinra inhibits the IL-1 receptor and has shown to prevent CRS as well as ICANS in a humanized mouse model.[36] Anakinra has been used at a dosage of 2-8 mg/kg BW/day via subcutaneous administration[47] and might be most effective when used early in the course of CRS or even as prophylactic agent, given that IL-1 has shown to precede IL-6 production.[36] Despite reports of clinical use of siltuximab and anakinra,[8,78,87,119] systematic evaluation of both agents is pending.

Prevention of CAR T-cell toxicity

The role of preemptive use of anti-IL-6 agents and corticosteroids to prevent CRS and/or ICANS still needs to be defined and the optimal time-point of anti-cytokine treatment is under investigation.[58,76,77] Nonetheless, strategies to reduce the occurrence of CAR T-cell-associated side-effects include risk-adapted CAR T-cell dosing, with lower doses administered to patients with high disease burden,[44,90] or approaches including fractionated CAR T-cell administration.[120]

Cytopenias

Grade ≥3 cytopenias are frequent after CAR T-cell therapy[1,15,60,121-123] and grade ≥3 febrile neutropenia occurred in 31% and 17% of patients treated within the ZUMA-1[14] and JULIET[13] trials, respectively. With CD19-specific CAR T cells, prolonged severe cytopenias beyond 30 days after administration are characteristically observed in approximately 30% of patients treated with axi-cel or tisa-cel[1,13,14,60] of which most tend to occur in a biphasic pattern.[122] Whereas early cytopenia has been attributed to the lymphodepleting chemotherapy,[122,124,125] the etiology of late cytopenias is less clear. Late cytopenias after CAR T-cell therapy have been associated with higher amounts of prior chemotherapy, severe CRS and prior hematopoietic cell transplantation (HCT).[32,60,122,123,125] CAR-specific immunobiology, perturbations in the chemokine milieu after CAR T-cell administration and a limited hematopoietic capacity in those patients who have undergone a prior HCT have been proposed as underlying causes.[32,122,123]

Treatment of anemia and thrombocytopenia is based on replacement of erythrocytes and platelets.

Granulocyte colony-stimulating factor (G-CSF) is frequently used to treat neutropenia and should be strongly considered in patients with prolonged neutropenia,[40,53,116] although data to formally define whether it can be safely used as standard of care in patients after CAR T-cell treatment or might potentiate the incidence or severity of CRS by activating immune cells are lacking.[80,116,126,127] Anecdotally, persistent cytopenia after CAR T-cell treatment has been resolved by transfusion of autologous[128] or allogeneic[123] stem cell supports.

Other toxicities associated with CAR T cells

Infusion reaction. Although infusion reactions immediately after CAR T-cell administration are infrequent and mainly a response to the CAR T-cell cryoprotectants, pre-medication with antihistamines and acetaminophen before CAR T-cell infusion is advised.[129] Because of potentially detrimental effects,[75] corticosteroids should not be used as CAR T-cell pre-medication.[127,130]

Tumor lysis syndrome. Due to lymphodepleting chemotherapy or direct CAR T-cell-mediated destruction of malignant cells, tumor lysis syndrome (TLS) is a potential adverse effect of CAR T-cell treatment that can result in life-threatening arrhythmias and renal failure.[88,131-133] TLS has been observed also in CAR T-cell patients without receiving prior lymphodepleting chemotherapy.[132,134,135] Hence, TLS prophylaxis per standard medical guidelines including hydration and prophylactic use of hypouricemic agents (allopurinol, rasburicase, febuxostat), particularly when treating patients with high tumor burden, should be employed before initiating lymphodepleting therapy or administering CAR T cells.[47,136,137]

Anaphylaxis and immunogenicity. Most CAR constructs contain non-human elements that confer a risk for allergic reactions or neutralization of clinical efficacy. Allergic reactions are uncommon and anaphylaxis after CAR T-cell treatment has been reported only after repeated CAR T-cell infusions.[138] On the other hand, pre-existing anti-murine antibodies against CD19-directed CARs have been detected in patients before CAR T-cell infusion with axi-cel[139] and tisa-cel.[140] Although rising titers of CD19 antibodies against CARs have been observed post-infusion, expansion, persistence and efficacy of CAR T cells remained unaffected.[141] Fully humanized CARs to reduce immunogenicity are under clinical evaluation.[142]

B-cell aplasia and hypogammaglobulinemia. Due to the on-target off-tumor effect of CD19-directed CAR T cells on normal B cells, B-cell aplasia and hypogammaglobulinemia are expected toxicities after CD19-directed CAR T-cell treatment. Prolonged B-cell aplasia up to 5 years after CAR T-cell treatment in ALL has been reported,[143] with longer B-cell aplasia observed after CAR T cells comprising 4-1BB as costimulatory domain.[1,144] B-cell levels can thus be used as pharmacodynamic biomarkers to evaluate persistence of CAR T cells. In fact, for ALL, the time to B-cell recovery has been associated with duration of remission.[1,60,140] In contrast, B-cell recovery in lymphoma can occur even when remission after CAR T-cell therapy is ongoing.[13,15,121,141,145]

Hypogammaglobulinemia resulting from B-cell aplasia can be associated with an increased risk of infections.[143,146] In pediatric patients, empiric immunoglobulin (Ig) replacement during B-cell aplasia is carried out on a standard basis.[1,87] In adults, antibody-secreting CD19-negative memory plasma cells that assume basic humoral immune function despite CAR T-cell treatment have been described,[22,121,147-149] and for adult patients different approaches of Ig replacement have been proposed.[7,34,88,148] Prospective data and long-term follow-up will be critical to standardize recommendations for immune reconstitution and IgG-replacement strategies after CAR T-cell therapy.

Infections and anti-infective prophylaxis. Due to immunodeficiency caused by the underlying disease, prior cytotoxic treatments, lymphodepleting therapy, anti-cytokine treatment of CRS and ICANS, neutropenia and hypogammaglobulinemia, patients after CAR T cells are at risk for infections. In fact, early and late infectious complications after CAR T-cell administration are common.[5,16,118,121,124,150] Formal risk factors for infections after CAR T-cell treatment include ALL as underlying disease, more than four prior chemotherapeutic treatment regimens, a baseline absolute neutrophil count (ANC) <500 cells/mm^3, higher dose of administered CAR T cells and severity of CRS.[4,114] Most commonly, bacterial and viral infections occur[4,124] although invasive fungal infections[118,151] and reactivation of latent DNA viruses, e.g. CMV,[5,121] EBV,[31] HBV,[152,153] have also been described.

Evidence-based guidelines for anti-infective prophylaxis are pending, although for all patients herpes simplex (HSV) and varicella zoster (VZV) prophylaxis and *Pneumocystis jirovecii* prophylaxis up to 1 year after CAR T cell treatment and/or until a CD4$^+$-T-cell count $>200/\mu l$ are recommended.[80,87,116,139,154] Fungal and bacterial prophylaxes are not administered universally after CAR T-cell treatment,[80,87] but should be strongly considered in neutropenic patients.[53,87]

Hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Hemophagocytic lymphohistiocytosis (HLH) associated with autoimmunity is referred to as macrophage activation syndrome (MAS).[155] HLH/MAS have been observed in patients following treatment with CAR T cells.[7,14,19,33,40,114] Because patients meeting criteria for grade 3 CRS often also meet diagnostic criteria[156] for HLH,[7,14,19,33,40,114,157] it was unclear whether HLH/MAS represents the end point of CRS hyperinflammation or a separate toxic entity. The ASTCT grading guidelines excluded HLH/MAS from the definition of CRS[51] and CAR T-cell-related HLH/MAS diagnostic criteria were defined (Table 6).[40] The incidence of CAR T-cell-associated HLH/MAS is unclear. Occurrence in 1% of CAR T-cell patients was reported,[40,158] although substantial underdiagnosis due to significant overlap with high-grade CRS must be assumed.[114]

Table 6. Diagnostic criteria of hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) adapted from criteria proposed by the CARTOX Working Group[40]

Diagnostic criteria HLH/MAS
Ferritin >10 000 ng/ml during CRS
AND two of the following:
Grade ≥3 liver toxicity[a] (increase in levels of bilirubin, aspartate aminotransferase or alanine aminotransferase)
Grade ≥3 kidney toxicity[a] (oliguria or increase in serum creatinine)
Grade ≥3 pulmonary edema[a]
Hemophagocytosis in the bone marrow or other organs

[a] Assessed by Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.[49]

In most cases, CAR T-cell-associated HLH/MAS has been shown to resolve with CRS treatment including corticosteroids and tocilizumab.[159,160] For refractory HLH/MAS, treatment with etoposide and intrathecal cytarabine or methotrexate has been proposed, but this is controversial.[40,114,158] Also, anti-IL-1 management with anakinra has been suggested as treatment option, but remains to be formally evaluated.[157]

Genotoxicity and secondary malignancies. Viral vectors involved in transduction of lymphocytes for CAR T-cell manufacturing comprise the risk of insertional mutagenesis (IM). Although IM has been observed when hematopoietic stem cells were transduced via retroviral[161-165] and lentiviral[166] vectors, no genotoxicity of gene transfer into differentiated cells, including T cells, has been reported to date. Also, no retrovirus-related transformational events in more than 500 cumulative follow-up years of patients treated with engineered T cells have been observed.[167,168] However, transduction of a leukemic B cell during CAR T-cell manufacturing resulted in relapse, progressive leukemia and eventually death of a patient with ALL.[169] Secondary malignancies including myelodysplastic syndrome, bladder cancer or non-melanoma skin cancer have been reported after CAR T-cell therapy,[15,16,118,170] although previous therapies in this highly pre-treated patient population might have contributed to the development of malignancy.

Overall, data on late toxicities of CAR T cells, including effects on the immune system (i.e. new occurrence or exacerbation of neurologic or autoimmune disorders), IM and/or secondary malignancies, will require longer observation periods. A follow-up of 15 years has been requested as part of the marketing authorization of commercially available CAR T cells.[171,172]

Conclusions and future directions

CAR T cells are currently reshaping the treatment landscape of r/r lymphoid diseases and are expected to become available for other hematologic entities and even solid tumors. As CAR T cell use expands, recognition of risk factors for associated toxicities is critical for patient safety. With growing clinical experience, management of CAR T-cell-associated toxicities is an evolving field. Current management strategies for minimizing adverse effects of CAR T-cell therapy emphasize continuous monitoring, rapid detection, and accurate intervention with supportive care, anti-cytokine or corticosteroid therapy. Ideally, prophylactic and/or preemptive strategies to avoid toxicities without affecting efficacy and predictors of toxicities will be identified in the near future.

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