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COMPLICATIONS OF CAR-T CELL THERAPY IN HEMATOLOGIC MALIGNANCIES — A CURRENT CLINICAL REVIEW OF TOXICITIES AND MANAGEMENT STRATEGIES

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ABSTRACT

Chimeric antigen receptor T-cell (CAR-T) therapy represents an innovative treatment for relapsed or refractory hematologic malignancies, such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma. Despite its significant clinical efficacy, CAR-T therapy is associated with a spectrum of toxicities resulting from the activation of the immune system.
This review summarizes current understanding of the mechanism, clinical presentation, and management of CAR-T–related complications. Particular attention is given to cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), hematologic toxicities, and infectious complications, as well as long-term effects such as B-cell aplasia and hypogammaglobulinemia.
Additionally, predictive biomarkers, such as inflammatory markers, cytokine profiles, and CAR-T expansion kinetics, are examined in relation to risk stratification and early treatment strategies. Understanding these mechanisms is necessary to improve patient safety and optimize clinical outcomes.
In conclusion, although CAR-T therapy is a significant progress in hemato-oncology, additional research is required to improve toxicity prediction models and develop safer, next-generation cellular therapies.

KEYWORDS

Chimeric Antigen Receptor T-cell Therapy (CAR-T); Cytokine Release Syndrome (CRS); Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS); Hematologic Toxicity; Immunotherapy; Biomarkers; B-cell Aplasia; Infectious Complications

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Introduction

Over the past decade, immunotherapy has significantly reshaped the treatment landscape of hematologic malignancies. In contrast to conventional chemotherapy or radiotherapy, which eliminate rapidly dividing cells in a largely non-selective manner, modern immunotherapeutic approaches aim to engage the patient's immune system in a more targeted and sustained way. Principal modalities in hemato-oncology include monoclonal and bispecific antibodies, immunomodulatory agents, and chimeric antigen receptor T-cell (CAR-T) therapy, which is the primary focus of this review.

CAR-T therapy, classified as an advanced therapy medicinal product (ATMP) (European Medicines Agency, 2014), combines elements of both cytotoxic T-cell–mediated and antibody-mediated immune responses (Gorovits & Koren, 2019). In this approach, the variable fragment of an antibody is covalently linked to intracellular signaling domains derived from the TCR complex, most commonly CD3ζ (Sermer & Brentjens, 2019). As a result, genetically modified T cells express a chimeric antigen receptor that enables antigen recognition independently of major histocompatibility complex (MHC) molecules, providing a functional advantage over physiological T-cell responses(Muhammad et al., 2017).

Acute lymphoblastic leukemia (ALL) in adults and diffuse large B-cell lymphoma (DLBCL) are hematologic malignancies with poor prognoses in cases of relapsed or refractory disease, despite intensive chemotherapy and immunochemotherapy regimens (Neelapu et al., 2017; Maude et al., 2018). The introduction of CAR-T therapy has expanded therapeutic options for these patients, enabling deep and durable remissions even in heavily pretreated populations. However, this efficacy is correlated with specific toxicities resulting from excessive immune activation (Neelapu et al., 2017; Maude et al., 2018).

The introduction of CAR-T therapy is widely considered a major breakthrough in the treatment of hematologic malignancies, particularly in patients with relapsed or refractory ALL and DLBCL (Neelapu et al., 2017; Maude et al., 2018). Such an approach has demonstrated high complete remission rates in relapsed or refractory DLBCL (40–60% CR) and improved survival outcomes compared with standard treatment

options (Lee et al., 2014). In the ELIANA trial, which included patients with relapsed or refractory B-cell ALL treated with tisagenlecleucel, the overall response rate reached 81%, with durable remissions and favorable overall survival outcomes (Lee et al., 2019). At the same time, such intense immune activation is associated with the risk of distinct, and occasionally severe, adverse events related to an exaggerated inflammatory response (Neelapu et al., 2018). Reported toxicities include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, cytopenias, and infections (Neelapu et al., 2018). Understanding the basic mechanisms underlying these complications and developing effective management strategies are necessary for the safe clinical implementation of such therapy.

The crucial evidence supporting CAR-T therapy in relapsed or refractory DLBCL derives from multicenter, single-arm phase II clinical trials, most notably the ZUMA-1 study, which evaluated axicabtagene ciloleucel in patients with heavily pretreated large B-cell lymphoma (Lee et al., 2014). The study demonstrated complete remission rates of approximately 40–60%, with sustained responses observed during long-term follow-up.

Similarly, the ELIANA trial, a global multicenter phase II study assessing tisagenlecleucel in pediatric and young adult patients with relapsed or refractory B-cell ALL, reported an overall response rate of 81%, with a high proportion of minimal residual disease-negative remissions and durable survival outcomes (Lee et al., 2019).

Safety analyses in these trials, as well as subsequent pooled evaluations and observed registries, consistently identified immune-mediated toxicities as characteristic complications of CAR-T therapy (Neelapu et al., 2018). The most frequently reported adverse events include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) (Munshi et al., 2021), prolonged cytopenias, and infectious complications (Neelapu et al., 2018).

Comprehending the immunopathophysiological mechanisms underlying these toxicities and designing standardized grading and management algorithms are central to the safe clinical implementation of CAR-T therapy.

This review summarizes current evidence on the incidence, pathophysiology, and management of CAR-T–related toxicities, with particular emphasis on patients with ALL and DLBCL.

Methodology

This article was prepared as a narrative review based on a comprehensive analysis of the current literature on CAR-T cell therapy–associated toxicities. Relevant publications were identified through searches of major biomedical databases, including PubMed, Scopus, and Web of Science.

The search strategy included combinations of keywords such as “CAR-T therapy”, “cytokine release syndrome”, “ICANS”, “neurotoxicity”, “hematologic toxicity”, and “CAR-T complications”. Preference was given to peer-reviewed clinical trials, meta-analyses, and high-impact review articles published primarily within the last decade.

Landmark studies, including pivotal clinical trials such as ZUMA-1, JULIET, and ELIANA, were specifically included due to their significant contribution to the understanding of both efficacy and safety profiles of CAR-T therapies.

Articles were selected based on their relevance to the topic, methodological quality, and clinical significance. No formal systematic review protocol or meta-analysis framework was applied; instead, the aim was to provide a structured and clinically meaningful synthesis of currently available evidence.

Mechanism of Action of CAR-T Cells

Physiological T lymphocytes are often unable to effectively eliminate malignant cells because their activation requires antigen recognition in the context of major histocompatibility complex (MHC) molecules (Sadelain et al., 2013). Tumor cells frequently downregulate MHC expression, thereby evading immune recognition and becoming functionally “invisible” to host T cells (June et al., 2018).

Chimeric antigen receptor (CAR) T cells are genetically engineered lymphocytes expressing a synthetic receptor composed of an extracellular single-chain variable fragment (scFv) derived from an antibody, fused to intracellular signaling domains derived from the T-cell receptor (TCR) complex, most commonly CD3ζ, together with one or more co-stimulatory domains (Lee et al., 2014). This design enables antigen recognition independently of MHC and directly couples tumor antigen binding to T-cell activation, proliferation, and cytotoxic effector function.

The manufacturing process includes collecting autologous T lymphocytes by leukapheresis, followed by ex vivo activation and expansion. A replication-deficient viral vector - most commonly a lentiviral or retroviral vector - is used to introduce the CAR construct into T cells. After genetic modification and expansion, CAR-T cells are reinfused intravenously and subsequently proliferate in vivo, mediating targeted lysis of tumor cells (Lee et al., 2014).

Three main generations of CAR constructs have been developed (June et al., 2018; Sadelain et al., 2013). First-generation CARs contain CD3ζ as the sole intracellular signaling domain. Second-generation CARs incorporate one co-stimulatory domain (e.g., CD28 or 4-1BB), enhancing expansion and persistence. Third-generation CARs include two co-stimulatory domains, further augmenting signaling intensity and functional activity (Lee et al., 2014).

Costimulatory Domains: CD28 versus 4-1BB and Their Impact on Toxicity

Second-generation CAR constructs incorporate either CD28 or 4-1BB (CD137) intracellular costimulatory domains, which strongly influence CAR-T expansion kinetics, persistence, and toxicity profiles. CD28-based CAR constructs, such as axicabtagene ciloleucel, are distinguished by rapid early expansion and high peak CAR-T cell levels, which have been associated with increased rates of early-onset CRS and neurotoxicity (Locke et al., 2019; Neelapu et al., 2023).

In contrast, 4-1BB–based constructs, including tisagenlecleucel and lisocabtagene maraleucel, typically demonstrate slower expansion kinetics but enhanced long-term persistence (Maude et al., 2018; Abramson et al., 2020). This difference in expansion dynamics may partially explain variations in toxicity severity and timing seen across products.

Comparative assessments suggest that CD28-costimulated products are associated with earlier CRS onset, whereas 4-1BB constructs may confer a more prolonged but generally less abrupt inflammatory profile (Locke et al., 2019; Abramson et al., 2020). However, cross-trial comparisons remain limited by heterogeneity in grading criteria and patient populations.

Importantly, persistence of 4-1BB–based CAR-T cells has been associated with prolonged B-cell aplasia, which may result in sustained hypogammaglobulinemia (Park et al., 2018). Thus, costimulatory domain selection influences not only efficacy, but also the temporal pattern and type of toxicity.

Future CAR designs intend to balance rapid tumor clearance with controlled cytokine release, potentially through optimized signaling intensity or incorporation of safety switches (Sadelain et al., 2017).

CAR-T Cell Therapy–Associated Cytokine Release Syndrome

Cytokine release syndrome (CRS) is the most common systemic adverse effect associated with CAR-T therapy and results from rapid immune activation and massive cytokine secretion (Lee et al., 2019; Norelli et al., 2018). It is characterized by a systemic inflammatory response initiated by activated CAR-T cells and secondary activation of monocytes/macrophages.

The pathophysiology of CRS involves elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6), interleukin-1 (IL-1), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) (Sadelain et al., 2017). IL-6 plays a central role, which forms the rationale for therapeutic blockade with tocilizumab (Neelapu et al., 2018).

Clinically, CRS presents with a spectrum of manifestations ranging from mild flu-like symptoms (fever, fatigue, myalgia, headache) to severe, life-threatening complications such as capillary leak syndrome, hypotension, disseminated intravascular coagulation, shock, acute respiratory distress syndrome (ARDS), and multiorgan failure (Neelapu et al., 2018; Sadelain et al., 2017).

Large clinical trials have quantified the incidence and severity of CRS and may persist beyond day 30 in a subset of patients. In the ELIANA trial (tisagenlecleucel in relapsed/refractory B-cell ALL), CRS occurred in 77% of patients, with 46% experiencing grade ≥3 CRS (Maude et al., 2018). In the ZUMA-1 trial (axicabtagene ciloleucel in refractory DLBCL), CRS was reported in 93% of patients, with grade ≥3 CRS in 13% (Neelapu et al., 2017). In the JULIET trial (tisagenlecleucel in diffuse large B-cell lymphoma), CRS occurred in 58% of patients, with grade ≥3 in 22% (Schuster et al., 2019). Risk factors for developing CRS include high tumor burden, high CAR-T cell dose, rapid CAR-T expansion, and younger age Maude et al., 2018; Gust et al., 2017; Hay et al., 2017).

CRS typically develops within 1-14 days after CAR-T infusion, with a median onset of 2-3 days, and resolves with supportive care and targeted therapy. Severity is graded according to the ASTCT consensus criteria, which rely on fever, hypotension, and hypoxia (Maude et al., 2018; Lee et al., 2019).

Neurological toxicity

Neurological toxicity is a further notable adverse effect associated with CAR-T cell therapy, commonly referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). Patients may present with a spectrum of acute neurological signs or symptoms, such as headache, confusion, delirium, language disturbances, seizures, and, in rare cases, severe cerebral edema, which represent some of the reported clinical manifestations (Siegler & Kenderian, 2020). Its incidence ranges from 40% to 67% in patients with leukemia and 30–62% in patients with lymphoma, depending on the CAR-T product and disease context (Maude et al., 2018; Locke et al., 2019; Abramson et al., 2020). ICANS typically occurs within 1 to 3 weeks after CAR-T cell infusion (Siegler & Kenderian, 2020). Some characteristics were identified as predictive of subsequent ICANS development, including: younger age, B-cell ALL, high bone marrow disease burden, high CAR-T cell dose, and any pre-existing neurologic comorbidity (Gust et al., 2017).

In a study by Santomasso et al., 53 patients treated with CD19-directed CAR-T cells were evaluated: 62.3% developed ICANS of any grade, with 11 patients experiencing mild symptoms and 22 developing severe neurological toxicity; no deaths were directly attributed to neurotoxicity (Santomasso et al., 2018).

Similarly, Rubin et al. (2019) analyzed 100 adult patients, predominantly with lymphoma. At least one neurotoxicity symptom was observed in 77 patients, with a median severity of grade 2. The most frequent manifestations were generalized encephalopathy (n=57) and headache (n=42), typically mild and self-limited. Tremor, asterixis, and myoclonus were reported in 39 patients. Five patients died after CAR-T therapy, with only one death directly related to neurotoxicity (Rubin et al., 2019).

Notably, ICANS often co-occurs with cytokine release syndrome (CRS); earlier onset and higher grade of CRS are associated with increased risk and severity of ICANS (Gust et al., 2017). The pathophysiology is thought to involve systemic cytokine elevation (IL-6, IL-1, IFN-γ), blood–brain barrier disruption, and endothelial activation (Lee et al., 2019). Current consensus grading of ICANS follows ASTCT criteria, which standardize severity assessment based on neurological examination, cognitive function, and level of consciousness (Lee et al., 2019).

Hematologic toxicities

Hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, are common complications following CAR-T cell therapy. Their incidence varies by disease and CAR-T product but is generally reported in 30–90% of patients, with severe (grade ≥3) cytopenias occurring in approximately 30–60% of cases (Jain et al., 2020; Fried et al., 2019).

Cytopenias typically develop within the first week after CAR-T infusion and may persist for several weeks, particularly in patients with prior extensive chemotherapy or high disease burden. The pathophysiology is multifactorial and includes the myelosuppressive effects of lymphodepleting chemotherapy, systemic inflammation mediated by cytokine release, and impaired bone marrow reserve (Maude et al., 2018).

Management is primarily supportive, including growth factor administration (e.g., G-CSF for neutropenia), transfusions for anemia or thrombocytopenia, and infection prophylaxis. Close monitoring is indispensable, given that prolonged cytopenias increase the risk of infectious complications (Hill & Seo, 2020).

Infectious complications

Infectious complications constitute a significant cause of morbidity following CAR-T cell therapy and are closely associated with prolonged cytopenias, B-cell aplasia, and prior intensive treatment. Infections occur in approximately 30–60% of patients within the first months after infusion, with a higher incidence observed in individuals who develop severe CRS or persistent neutropenia (Neelapu et al., 2018; Hill et al., 2018; Hill & Seo, 2020).

Early infections (within the first 30 days) are predominantly bacterial, reflecting profound neutropenia and mucosal barrier injury related to lymphodepleting chemotherapy. In contrast, viral infections (including herpesviruses and respiratory viruses) and opportunistic fungal infections are more frequently observed later in the disease course, particularly in patients with prolonged immunosuppression (Park et al., 2018).

In the ZUMA-1 trial evaluating axicabtagene ciloleucel in relapsed/refractory DLBCL, grade ≥3 infections were reported in approximately 23% of patients (Neelapu et al., 2017). Similarly, in the ELIANA trial assessing tisagenlecleucel in B-cell ALL, infections of any grade occurred in more than half of treated patients, with severe infections observed in a substantial minority(Maude et al., 2018).

An important contributor to late infectious risk is prolonged B-cell aplasia and hypogammaglobulinemia resulting from CD19-targeted therapy. Management strategies include antimicrobial prophylaxis, immunoglobulin replacement therapy in selected patients, and careful long-term monitoring (Neelapu et al., 2018).

Hypogammaglobulinemia and B-Cell Aplasia

A characteristic on-target, off-tumor effect of CD19-directed CAR-T therapy is prolonged B-cell aplasia, resulting from the elimination of normal CD19-expressing B lymphocytes. As CD19 is expressed not only on malignant but also on healthy B cells, CAR-T cells cannot distinguish between these populations. Consequently, persistent depletion of B cells may occur and persist for months or even years after infusion (Neelapu et al., 2018).

B-cell aplasia frequently leads to hypogammaglobulinemia, particularly reduced serum IgG levels, thereby raising susceptibility to recurrent and opportunistic infections. In the long-term follow-up of patients treated with CD19 CAR-T cells for B-cell ALL, sustained B-cell aplasia was observed in a substantial proportion of responders and was associated with durable CAR-T persistence (Park et al., 2018). Similarly, in studies involving patients with relapsed or refractory DLBCL, hypogammaglobulinemia was commonly reported during follow-up and required immunoglobulin replacement in selected cases (Schuster et al., 2019).

Although B-cell aplasia is considered a biomarker of ongoing CAR-T activity and treatment efficacy, it requires long-term monitoring of immunoglobulin levels. Management includes periodic assessment of serum IgG concentrations and administration of intravenous or subcutaneous immunoglobulin (IVIG/SCIG) in patients with severe or recurrent infections (Neelapu et al., 2018).

Management of CAR-T–Related Toxicities

The successful clinical implementation of CAR-T therapy requires early recognition and prompt management of treatment-related toxicities. Current management strategies are guided primarily by the consensus recommendations of the American Society for Transplantation and Cellular Therapy (ASTCT) (Lee et al., 2019) and by pivotal clinical trials evaluating CD19-directed CAR-T products (Neelapu et al., 2018).

Management of Cytokine Release Syndrome (CRS)

Management of CRS is based on ASTCT consensus grading criteria (Lee et al., 2019).

Supportive care is sufficient for grade 1 CRS and includes antipyretics, intravenous fluids, and close monitoring (Neelapu et al., 2018).

For grade ≥2 CRS, IL-6 blockade with tocilizumab is recommended as first-line therapy (Lee et al., 2019). Tocilizumab has demonstrated rapid reversal of fever and hypotension without impairing CAR-T expansion or antitumor efficacy (Maude et al., 2018; Neelapu et al., 2018).

Corticosteroids are indicated in patients with severe or refractory CRS or inadequate response to tocilizumab (Gust et al., 2017). Recent data suggest that short-term corticosteroid use does not substantially impair CAR-T clinical efficacy (Maude et al., 2018).

In grade 3-4 CRS, management requires intensive care support, including vasopressors, oxygen supplementation, or mechanical ventilation (Neelapu et al., 2018).

Emerging evidence supports IL-1 blockade (anakinra) in refractory CRS and severe hyperinflammatory states, particularly when macrophage activation is suspected (Siegler & Kenderian, 2020).

Management of ICANS

Unlike CRS, tocilizumab has limited therapeutic effect in isolated ICANS due to poor blood–brain barrier penetration (Lee et al., 2019).

Corticosteroids are the first-line treatment for grade ≥2 ICANS (Lee et al., 2019). Dexamethasone is typically used for moderate neurotoxicity, while high-dose methylprednisolone is recommended in severe cases or cerebral edema (Gust et al., 2017).

Seizure prophylaxis with levetiracetam is commonly administered, and severe cases require ICU monitoring (Santomasso et al., 2018).

Endothelial activation and blood–brain barrier disruption have been implicated in ICANS pathophysiology, supporting the rationale for investigational anti-inflammatory approaches (Santomasso et al., 2018).

Management of Hematologic Toxicities

Prolonged cytopenias beyond day 30–90 after infusion are well described (Neelapu et al., 2018; Gust et al., 2017).

Management includes:

- red blood cell and platelet transfusions
- granulocyte colony-stimulating factor (G-CSF), typically after CRS resolution (Neelapu et al., 2018)
- bone marrow evaluation in persistent cytopenias

These toxicities are frequently multifactorial, resulting from lymphodepleting chemotherapy, marrow exhaustion, and exposure to inflammatory cytokines (Gust et al., 2017).

Management of Infectious Complications

Infectious complications arise from prior immunosuppression, cytopenias, and B-cell aplasia (Neelapu et al., 2018; Hill & Seo, 2020).

Current expert recommendations include (Hill & Seo, 2020):

- antibacterial prophylaxis during neutropenia
- antiviral prophylaxis (HSV/VZV)
- Pneumocystis jirovecii prophylaxis
- antifungal prophylaxis in high-risk patients

Febrile neutropenia requires immediate empirical broad-spectrum antibiotics, as differentiation from CRS may be clinically challenging (Neelapu et al., 2018).

Management of Hypogammaglobulinemia and B-Cell Aplasia

CD19-targeted CAR-T therapy induces B-cell aplasia and secondary hypogammaglobulinemia (Neelapu et al., 2018).

Regular monitoring of immunoglobulin levels is recommended, and intravenous immunoglobulin (IVIG) replacement should be considered in patients with recurrent infections or significantly reduced IgG levels (Hill & Seo, 2020).

Persistent B-cell aplasia is considered a pharmacodynamic marker of CAR-T activity (Neelapu et al., 2018).

Predictive Biomarkers of CAR-T–Associated Toxicities

The identification of predictive biomarkers for CAR-T–related toxicities is a field of intense clinical investigation. Early recognition of patients at high risk for severe cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) may allow preemptive intervention and improved safety, free of impairing antitumor efficacy.

Baseline Disease Burden

High tumor burden at the time of CAR-T infusion has consistently been associated with an increased risk of severe CRS and ICANS. In both acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL), elevated bone marrow blast percentage or bulky nodal disease correlates with enhanced CAR-T expansion and higher peak cytokine levels (Hay et al., 2017; Locke et al., 2019).

Hay et al. demonstrated that patients with higher pre-infusion disease burden exhibited greater in vivo CAR-T proliferation and significantly increased rates of grade ≥3 CRS (Hay et al., 2017). Similarly, in the ELIANA and ZUMA-1 cohorts, tumor burden appeared as a major determinant of toxicity severity (Neelapu et al., 2017; Maude et al., 2018). The results support risk-adapted approaches, including cytoreductive bridging therapy before CAR-T infusion.

CAR-T Cell Expansion Kinetics

The magnitude and kinetics of CAR-T cell expansion are among the most reproducible predictors of toxicity. Rapid early expansion, primarily within the first 3-5 days post-infusion, is strongly associated with severe CRS and ICANS (Hay et al., 2017; Turtle et al., 2016).

Peak CAR transgene levels in peripheral blood correlate with cytokine surge intensity, especially IL-6 and IFN-γ concentrations (Turtle et al., 2016). CD28-costimulated CAR constructs typically exhibit more rapid expansion than 4-1BB–based products, which may partially explain the higher early toxicity rates observed with CD28-based therapies (Sadelain et al., 2017).

Quantitative PCR-based monitoring of CAR transgene levels may therefore act not only as a pharmacodynamic marker of therapeutic effect but also as an early warning indicator for impending severe toxicity.

Inflammatory Markers: CRP and Ferritin

Among routinely available laboratory parameters, C-reactive protein (CRP) and ferritin are widely used surrogate biomarkers of systemic inflammation. Elevated early CRP levels after CAR-T infusion correlate with CRS severity, reflecting IL-6–mediated hepatic acute-phase responses (Lee et al., 2014).

Hyperferritinemia has been associated with severe CRS and macrophage activation-like syndromes (Gust et al., 2017). Extremely high ferritin levels may indicate excessive monocyte/macrophage activation, a key driver of CRS pathophysiology. Although neither CRP nor ferritin alone possesses sufficient specificity to serve as a standalone predictor, their progressing trends can support early clinical decision-making.

Cytokine Profiles

Direct measurement of cytokine concentrations has provided mechanistic insight into CAR-T-associated toxicities. Elevated IL-6, IL-1, IFN-γ, and TNF-α levels are hallmarks of CRS (Gust et al., 2017; Norelli et al., 2018). Norelli et al. and Giavridis et al. demonstrated that monocyte-derived IL-1 and IL-6 are central mediators of systemic inflammatory response, and IL-1 blockade mitigated CRS severity in preclinical models (Gust et al., 2017; Giavridis et al., 2018).

Higher early serum IL-6 concentrations have been associated with progression to severe CRS, supporting the rationale for early tocilizumab intervention in high-risk patients (Lee et al., 2019; Gust et al., 2017). However, routine cytokine profiling remains limited by availability, cost, and turnaround time in most clinical settings.

Endothelial Activation Markers

Endothelial dysfunction has been recognized as a key component of the pathophysiology of both CRS and ICANS. Elevated levels of angiopoietin-2 (Ang-2), von Willebrand factor (vWF), and markers of capillary leak have been observed in patients who subsequently develop severe neurotoxicity (Gust et al., 2017; Nastoupil et al., 2020).

Gust et al. demonstrated that patients with high Ang-2/Ang-1 ratios prior to CAR-T infusion were at increased risk for ICANS, denoting a preexisting endothelial vulnerability state (Gust et al., 2017). These data support the concept that endothelial activation may represent a mechanistic link between systemic inflammation and blood–brain barrier disruption.

Although not yet implemented in routine practice, endothelial biomarkers may contribute to future predictive risk models.

Hematologic and Metabolic Parameters

Baseline cytopenias, elevated lactate dehydrogenase (LDH), and markers of high tumor turnover have also been associated with increased toxicity risk (Park et al., 2018). Elevated LDH reflects aggressive disease biology and may correlate with rapid CAR-T expansion and inflammatory amplification.

Moreover, preexisting thrombocytopenia and coagulopathy have been linked to more severe CRS, possibly reflecting baseline endothelial activation or impaired marrow reserve (Jain et al., 2020).

Composite Risk Models

Given the multifactorial nature of CAR-T toxicities, single biomarkers are unlikely to provide sufficient predictive effectiveness. Composite models uniting tumor burden, CAR-T expansion kinetics, inflammatory markers (CRP, ferritin), cytokine levels, and clinical parameters (age, performance status) may offer greater predictive value (Turtle et al., 2016; Jain et al., 2020).

Recent real-world analyses suggest that dynamic risk stratification within the first 48-72 hours after infusion may allow early corticosteroid initiation in selected high-risk patients without impairing long-term remission rates (Nastoupil et al., 2020).

Future Directions in Biomarker Development

Emerging strategies include:

- Early transcriptomic profiling of infused CAR-T products
- Assessment of T-cell exhaustion markers
- Host genetic polymorphisms affecting cytokine signaling.
- Machine learning–based predictive algorithms incorporating clinical and laboratory data (Pennisi et al., 2020)

Prospective validation of biomarker-guided intervention approaches will be essential before broad implementation. Ultimately, personalized toxicity prediction may enable safer outpatient administration of CAR-T and broader patient eligibility.

Table 1. Biomarkers

Biomarker	Associated Toxicity	Mechanistic Rationale	Clinical Utility	Key References
High baseline tumor burden	Severe CRS, ICANS	Increased CAR-T expansion and cytokine surge	Risk stratification before infusion	[4], [6], [20], [21]
Rapid CAR-T expansion kinetics	Severe CRS, ICANS	High peak cytokine release (IL-6, IFN-γ)	Early toxicity prediction	[20], [22]
Elevated CRP (early post-infusion)	CRS severity	IL-6–mediated acute-phase response	Easily accessible surrogate marker	[9]
Hyperferritinemia	Severe CRS, macrophage activation	Monocyte/macrophage hyperactivation	Supportive inflammatory marker	[24]
Elevated IL-6 levels	CRS	Central cytokine driver	Rationale for tocilizumab therapy	[9],[10]
Elevated IL-1	CRS, ICANS	Monocyte-driven inflammation	Potential target for anakinra	[25], [26]
High Ang-2 / Ang-1 ratio	ICANS	Endothelial activation, BBB disruption	Emerging neurotoxicity biomarker	[12]
Elevated LDH	Severe CRS	High tumor turnover	Baseline risk indicator	[21]
Baseline cytopenias	Prolonged hematologic toxicity	Reduced marrow reserve	Post-infusion monitoring	[26]

As shown in Table 1, no single biomarker provides sufficient predictive accuracy; rather, composite risk models uniting tumor burden, inflammatory markers, and CAR-T expansion kinetics appear most promising.

Discussion

CAR-T cell therapy has undoubtedly changed the therapeutic landscape of relapsed or refractory B-cell malignancies, particularly in patients with otherwise limited treatment options. However, the benefits of this approach are closely linked to a distinct and sometimes challenging toxicity profile.

In contrast to conventional cytotoxic therapies, many of the toxicities observed after CAR-T infusion are directly related to its mechanism of action and the intensity of immune activation. Rapid in vivo expansion and cytokine amplification, while necessary for tumor control, contribute to the development of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). This creates a clinical challenge, as strategies aimed at reducing toxicity must be carefully balanced against the risk of compromising antitumor activity.

Although crucial trials such as ZUMA-1, JULIET, and ELIANA demonstrated manageable safety profiles, most were single-arm studies conducted in specialized centers. Real-world analyses have confirmed

overall reproducibility of efficacy outcomes, yet have additionally highlighted variability in toxicity management practices across institutions (Nastoupil et al., 2020; Abramson et al., 2020). Standardization of early intervention protocols is necessary, particularly as CAR-T therapy expands into earlier treatment lines.

Long-term complications, including prolonged cytopenias, sustained B-cell aplasia, and hypogammaglobulinemia, raise important questions regarding chronic immune dysregulation. The biological mechanisms underlying delayed hematologic recovery are incompletely understood and may involve inflammation-mediated marrow suppression and baseline hematopoietic exhaustion.

Emerging strategies to improve safety include modulation of CAR signaling strength, incorporation of suicide switches, dual-antigen targeting, and exploration of allogeneic or CAR-NK platforms. Furthermore, integrating predictive biomarkers into clinical algorithms may enable personalized dosage strategies and facilitate safe outpatient administration.

As CAR-T therapies move beyond CD19-directed constructs into BCMA-targeted and next-generation platforms, comparative safety profiling will become increasingly important. A greater understanding of costimulatory domain biology, endothelial activation pathways, and host inflammatory predisposition may ultimately allow refinement of toxicity risk models.

Overall, continued translational research and harmonization of management guidelines will be vital to maximizing therapeutic benefit while limiting treatment-related morbidity.

Conclusions

Chimeric antigen receptor T-cell (CAR-T) therapy is now widely regarded as one of the most important advances in the treatment of relapsed or refractory hematologic malignancies, particularly acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). By enabling a major histocompatibility complex–independent tumor recognition and sustained cytotoxic activity, CAR-T therapy has achieved deep and durable remissions in heavily pretreated patient populations.

However, this notable efficacy is accompanied by a distinct toxicity profile resulting from profound immune activation. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) represent the most clinically significant early complications, whereas prolonged cytopenias, infectious complications, and hypogammaglobulinemia contribute to intermediate- and long-term morbidity. The introduction of standardized grading systems and consensus-based management algorithms, particularly those developed by the American Society for Transplantation and Cellular Therapy (ASTCT), has substantially improved the safety and predictability of CAR-T therapy in routine clinical practice.

Early recognition of toxicity, risk-adapted intervention with targeted immunomodulatory agents such as tocilizumab and corticosteroids, and multidisciplinary supportive care constitute important elements of optimal management. Importantly, accumulating evidence indicates that appropriate toxicity control does not necessarily compromise antitumor efficacy, highlighting the feasibility of sustaining safety with therapeutic benefit.

As CAR-T technologies continue to evolve, future efforts will emphasize refining patient selection, improving toxicity-prediction models, and developing next-generation constructs to augment therapeutic effect while limiting adverse effects. Real-world evidence and long-term follow-up studies will be essential to better define the durability of responses, late complications, and overall quality-of-life outcomes.

In conclusion, CAR-T therapy is widely considered one of the most significant advances in modern hemato-oncology. Further improvements in toxicity management, together with a better understanding of underlying immunopathophysiological mechanisms, will likely determine how broadly and safely this therapy can be implemented in the future.

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