CAR T Cell Therapy in Hematology: Navigating Toxicities and Deciphering Patient Experiences Through Patient-Reported Outcomes

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ABSTRACT:
This review examines the role of Patient-Reported Outcomes (PROs) in measuring toxicities of Chimeric Antigen Receptor T Cell Therapy (CAR-T) for hematological malignancies. While highlighting the complex task of understanding the pathophysiology of CAR T’s unique adverse events (AEs), the discussion focuses on the need for precise characterization of the diverse symptomatology associated with individual CAR T syndromes and the importance of capturing patient experiences with these side effects using PRO instruments. This review underscores the continuous search for an ideal PRO tool that is effective in detecting both early changes and late toxicities; stressing the importance of monitoring PROs soon after therapy to gather data on acute toxicity, enabling timely interventions that could reduce symptom severity. The assessment of PROs at later stages is also highlighted as crucial for evaluating long-term quality of life (QoL), especially in terms of neurocognitive effects. The narrative review identifies a gap in current PRO tools not specifically tailored for CAR T therapy and calls for further research to develop a comprehensive set of symptoms for monitoring in various studies. Such efforts are vital for improving our understanding of therapy tolerability as well as for improving the treatment of these side effects. This would also enable the comparison of different CAR T products based on their response rates.

KEYWORDS: Immunotherapy, Adoptive, Patient Reported Outcome Measures, Hematologic Neoplasms, Drug-Related Side Effects and Adverse Reactions

SAŽETAK:
CAR T stanična terapija u hematologiji: upravljanje toksičnostima i dešifriranje iskustava pacijenata putem ishoda koje su prijavili pacijenti

U ovom preglednom radu istražujemo ulogu Patient-Reported Outcomes (PROs) u analizi i upravljanju toksičnosti terapije CAR T stanicama u liječenju hematoloških malignih bolesti. CAR T stanična terapija otvara nove horizonte u liječenju, ali istovremeno predstavlja izazov zbog svojih specifičnih i varijabilnih nuspojava. Ovim radom pokušali smo ukazati na važnost razumijevanja patofiziologije CAR T terapije i potrebu za razvojem PRO instrumenata. Ovi alati su esencijalni za učinkovito prikupljanje podataka o kratkoročnoj toksičnosti, što može značajno doprinijeti prevenciji i
Introduction - Brief Overview of CAR T-cell Therapy:

With the recent success of Chimeric Antigen Receptor T-Cell Therapy (CAR T), many researchers have delved into understanding the mechanisms and characteristics that determine this modality's efficacy and toxicity. The concept of chimeric T cell receptors dates back 35 years to Dr. Yoshikazu Kurosawa and Dr. Zelig Eshhar's teams, who pioneered the redirection of T cells to target antigens in cancer treatment. (1, 2) CAR-T therapy uses modified T cells to target antigens on tumor cells, leading to their elimination and tumor clearance. These T cells, often derived from the patient (autologous) or a donor (allogeneic), are equipped with a Chimeric Antigen Receptor (CAR) to bind specific antigens. The evolution of CAR-T began with first-generation CARs, featuring a basic T-cell activating domain. Second-generation CARs added costimulatory domains to enhance function and longevity, and third-generation CARs incorporated multiple domains for improved signaling and anti-tumor effects. Fourth-generation CARs further advanced by modulating the tumor environment via specific cytokine secretion. (3-5)

Current Status in Hematologic Malignancy

CAR T marks a significant advancement for treatment of hematologic malignancies, demonstrating remarkable efficacy, particularly in relapsed/refractory (R/R) B-cell malignancies. Currently, CD19 and B-cell maturation antigen (BCMA) stand as the predominant tumor-associated targets in this therapeutic approach. The US Food and Drug Administration (FDA)'s first approval for CAR T was for tisagenlecleucel (tisa-cel), granted in 2017, in treatment of pediatric and young adults up to 25 years of age with B-cell acute lymphoblastic leukemia (B-ALL). These products are axicabtagene ciloleucel (axi-cel), tisa-cel, lisocabtagene maraleucel (liso-cel) and brexucabtagene autoleucel (brexu-cel). The other two, targeting BCMA, are used for treatment of multiple myeloma (MM) - idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilt-a-cel). (6, 7) The emergence of novel toxicities associated with CAR T products has underscored the importance of PROs in capturing and understanding these unique adverse events. This patient-centric approach is vital for a holistic understanding of the efficacy and safety of CAR T, ensuring that treatment advancements truly align with patient well-being. As such, PROs are instrumental in shaping the development, evaluation, and refinement of these innovative therapies. In this narrative review we concentrate on the challenges posed by toxicities in CAR T for hematological malignancies, emphasizing the use of PROs. There is a limited amount of such reviews and research focusing on PROs in the context of CAR T. This review seeks to fill this gap, offering a contribution to a field where extensive analysis is currently sparse.

Overview of toxicities:

With CAR-T being a novel therapeutic approach, clinicians and patients alike have adjusted to a learning curve of a new class of toxicities introduced called immune effector cell (IEC)-associated toxicities. The most frequently observed adverse events (AEs) from CAR T, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), continue to pose challenges to the broader application of this type of treatment and in everyday clinical practice since they require close inpatient monitoring by a multidisciplinary team of specialists. Additional AEs associated with CAR T include cytopenias, infections, tumor lysis syndrome (TLS), hypogammaglobulinemia, immune effector cell (IEC) associated HLH-like syndrome (IEC-HS), infusion-related reactions and anaphylaxis, secondary malignancies, and even graft-versus-host disease (GVHD). Data about the long-term consequences of therapy is particularly lacking, and in that aspect, PROs play an
especially important role. This is of particular importance, since CAR T is now being introduced earlier in the treatment algorithm (8).

**CRS**

The American Society for Transplantation and Cellular Therapy (ASTCT) defines CRS as “a supraphysiological response following any immunotherapy that results in the activation or engagement of endogenous or infused T-cells and/or other immune effector cells” (9). It is a type of non-antigen-specific toxicity that arises from intense immune system activation. CRS is a common occurrence in most patients with ALL, with prevalence varying widely, ranging from 25% to 100%, depending on severity.(10, 11) CRS is the most common complication associated with CAR T. However, it occurs less frequently in patients receiving CAR T for other conditions like NHL and MM.(12)

As the name suggests, CRS revolves around the role of cytokines and its pathogenesis is not fully understood nor predictable. The term cytokine storm was first used in a scientific article on graft-versus-host disease (GvHD) over 30 years ago, marking the beginning of our understanding of this phenomenon (13). CRS is triggered by the release of specific cytokines, including interferon-gamma, interleukin-1 (IL-1), IL-6, IL-10, TNF-alpha and many others, primarily by activated T cells or tumor cells. This surge in proinflammatory cytokines leads to a widespread systemic inflammatory reaction, involving not only T cells but also macrophages, monocytes, dendritic cells and endothelial cells. (14, 15) The gasdermins (GSDME), pore-forming effector proteins that cause a lytic pro-inflammatory type of cell death also play a role in CRS, and animal experiments have shown that knocking down GSDME, destroying macrophages, or blocking the activation of GSDME prevents the development of CRS. (16, 17) CRS is not limited to patients undergoing cellular immunotherapy but can also affect those treated with bispecific antibodies and haploidentical allogeneic stem cell transplantation. Interestingly, a similar syndrome, akin to CRS, has been observed in patients with infectious diseases and became more widely known during the H5N1 influenza virus pandemic as well as during recent COVID19 pandemic. (18, 19)

The severity of CRS has been linked to several factors, including disease burden, quantity of CAR T-cells administered, level of T cell activation, specific molecular configuration of the CAR such as the costimulatory domain, type and intensity of lymphodepletion (LD) carried out before infusion. (20-22) Clinically, CRS is diagnosed by the presence of fever (≥38.0°C), which may be accompanied by varying degrees of hypotension, hypoxia, capillary leak and/or other signs of organ dysfunction, typically occurring between 1-14 days following CAR-T infusion. (9, 23) Originally, CRS severity was assessed using National Cancer Institute’s Common Terminology for Adverse Events (NCI CTCAE) version 4.03, but this method proved inadequate for evaluating this specific adverse effect of new cancer treatment. Subsequently, alternate scales like the Penn scale and the Lee scale were introduced. The ASTCT, aiming for a standardized approach, recommended a grading system for CRS, drawing on insights from a diverse group of experts. This system is designed for application in various clinical trials and settings following treatment approval. This consensus’ approach is based largely on the type of interventions that are required for patient management and grades patients into 4 groups – grade 3 and 4 requiring ICU care. (9, 24, 25) Laboratory markers can also be useful when attempting to identify the onset of CRS in a clinical setting. However, all of these markers, such as C-reactive protein (CRP), ferritin, however are non-specific and not reliable markers for diagnosing CRS. (26)

**ICANS**

Another major IEC-related toxicity is neurotoxicity referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS often presents as neurologic dysfunction, and can start with subtle changes such as word-finding difficulties, disorientation, issues with language comprehension and expression/expressive aphasia, difficulties with precise hand movements, tremors and drowsiness, but progress to more significant manifestations such as seizures and motor weakness.(27) The incidence of ICANS, similarly to CRS, demonstrates substantial variability, evidenced by reported frequencies ranging from 2% to 70%. (28, 29) Neurological manifestations usually commence between 3 to 6 days following CAR T infusion (30, 31). Factors indicative of a higher likelihood of developing ICANS include younger patient age, diagnosis of B-ALL, significant disease burden in the bone marrow, higher CAR T-cell dose, any prior neurological comorbidities, as well as the use of CAR T-cells that incorporate CD28 costimulatory domains.(31, 32) The underlying mechanisms of the pathophysiology of ICANS are still not well understood. In animal models, pathophysiology is hypothesized to involve endothelial cell activation and subsequent disruption of the blood-brain barrier, culminating in direct neuronal injury. Evidence supports the occurrence of vascular permeability in patients with severe ICANS. Furthermore, there are documented alterations in the angiopoietin (ANG)–TIE2 axis, a regulatory mechanism for endothelial cell activity under normal physiological conditions, that are also seen with sepsis.(33, 34) Additional evidence indicates the accumulation of von Willebrand Factor (vWF) multimers in patients experiencing severe ICANS, leading to coagulopathy (35). This process is compounded by the action of multiple pro-inflammatory cytokines. Extensive clinical research has demonstrated a significant correlation between augmented serum levels of a range of cytokines and the increased propensity for ICANS onset, including IL-2, IL-6, IL-10, IL-15 and GM-CSF.(28, 31, 34) Furthermore, in pathophysiology of ICANS, the antigens expressed by CNS cells are potentially also important. A recent
study revealed that human brain mural cells express CD19. This finding suggests that an OTOT effect might play a role in the neurotoxicity linked with CD19 CAR T-cells. However, ICANS has been reported in CAR T-cell treatments targeting not only CD19, suggesting that the occurrence of ICANS is not solely attributable to the specific target antigen, indicating the likelihood of an alternative mechanism at play. (36-38) As well as for CRS, ASTCT issued guidelines for grading ICANS based on several criteria, including the immune effector cell-associated encephalopathy (ICE) score, alterations in consciousness level, seizure occurrences, motor symptoms, and the presence of cerebral edema. (9)

**Cytopenias**

Post-CAR T cytopenia represents a multifaceted medical issue, demanding a holistic approach in management. Terminology related to post-CAR T cytopenias includes Persistent Cytopenia after T-cell Therapy (PCTT), CAR-T-POPENIA, and Immune Effector Cell Associated Hematotoxicity (ICAHIT), with classifications typically following NCI-CTCAE v5.0. (39-41) A joint effort by EHA and EBMT led to the development of best practice recommendations and a classification system for ICAHT, based on the depth and duration of neutropenia, for both early and late cytopenias, with 30 days post-infusion being the cutoff between the two. (41) Determining the precise incidence of cytopenias post-CAR T remains challenging due to its variable range, although early cytopenias are more common than late-onset ones. (42) A 2021 study by Rejeski et al. introduced the CAR-Hematotoxicity (MATOTOX) risk score, a tool for identifying patients at increased risk for prolonged cytopenias and severe infectious complications following CAR T. This study identified baseline cytopenias, high tumor burden, and elevated serum/plasma inflammatory markers as significant indicators of post-CAR T cytopenia. (43) CAR-T-cell infusion is typically preceded by LD chemotherapy, usually with agents like fludarabine and cyclophosphamide, which account for most early cytopenias. As LD chemotherapy is non-myeloablative, blood counts often recover rapidly. (44, 45) The etiology of late-onset cytopenias in CAR T-cell treatment is however multifactorial and complex. It may result from direct bone marrow inhibition by CAR T-cells or secondary to elevated inflammatory cytokine levels, as well as from bone marrow failure triggered by the immune system, as occurs in IEC-HS or due to the immune consequences of infections. Additionally, it is noteworthy that in both standard care and clinical trial settings for CD19- and BCMA-directed CAR T therapies, there is a significant association between prolonged cytopenia and severe manifestations, specifically grade 3 to 4 CRS or ICANS. (46)

**CAR-HLH/ IEC-HS**

To improve patient outcomes and establish a framework for investigating and comprehending the HLH-like syndrome in CAR T patients, a panel was initiated under the auspices of the ASTCT (47). Following CAR T, toxicities resembling hemophagocytic lymphohistiocytosis (HLH) occur, which are now identified as immune effector cell (IEC) associated HLH-like syndrome (IEC-HS). HLH is generally classified into two types: primary (genetic or inherited) and secondary (acquired). While familial (primary) HLH, a significant subtype of HLH in children, can also manifest in young adults, secondary HLH (sHLH) is overwhelmingly more prevalent in adults. (48, 49) sHLH in the context of CAR T has been reported with an incidence of about 3-4% (50). The pathogenesis of IEC-HS is likely attributable to dysregulated T-cell activation and an overly intense hyperinflammatory response after CAR T-cell infusion. The ASTCT panel ultimately defined IEC-HS as the emergence of a pathological and biochemical hyperinflammatory syndrome characterized by symptoms of macrophage activation/HLH, resulting from IEC therapy, and as a condition that is associated with the development or worsening of cytopenias, high ferritin levels, coagulopathy with low fibrinogen, and/or elevated liver enzymes. (47) Both CRS and IEC-HS display signs such as cytopenias, high ferritin levels, coagulation disorders, and elevated triglyceride levels. While patients with severe CRS often exhibit HLH-like symptoms, IEC-HS can present later, often emerging as CRS symptoms are resolving. Criteria for diagnosing IEC-HS are characterized by mention clinical and laboratory indicators, such as increased ferritin levels, emergence post-resolved CRS or escalating inflammatory response despite CRS treatment, liver enzyme elevation, low fibrinogen levels, histopathological evidence of hemophagocytosis, cytopenias, fever, and other signs and symptoms of organ failure. Different studies of various CAR T therapies have suggested different ferritin cutoff values as a criterion for the diagnosis of IEC-HS. (51-53) Due to the challenges in defining specific cutoffs, the ASTCT avoided setting exact ferritin levels in their criteria. However, a significant increase or rapid escalation in ferritin levels is essential for diagnosing IEC-HS. If inflammation persists with normal ferritin values, it should prompt the exploration of other possible causes. Clinically, while fever is a key diagnostic criterion for HLH in HLH-2004 diagnostic guidelines and can be observed in IEC-HS, ASTCT omitted fever from the proposed diagnostic criteria for IEC-HS in order to prevent confusion, as it is crucial to distinguish it from the onset or resurgence of CRS. (47, 49) Cytokine profiling could offer more understanding of the pathophysiology and diagnosis of IEC-HS, although this might be affected by previous CRS and treatments. In the future, integrating cytokine profiling into diagnostic procedures for IEC-HS could be beneficial and warrants further exploration. A study by Lichenstein et al. demonstrated that patients receiving CD22 CAR T cells who developed IEC-HS exhibited distinct cytokine patterns over time in comparison with CRS, specifically with cytokines like IFNγ, IL-1β, IL-6, IL-18, its binding protein, and MIP-1α. (53) The ASTCT panel
The prevention and management of delayed toxicities are becoming increasingly recognized as crucial elements in the care of patients who have been treated with CAR T. While the early toxicities of CAR T, such as CRS and ICANS, are well-documented syndromes in the literature, there is a noticeable absence of consolidation of knowledge on the observed and potential delayed effects of CAR T. The most common late effects of CAR T are hypogammaglobulinemia (B-cell depletion), prolonged cytopenias, infections, neurological and psychiatric disorders, secondary malignancies, and rarely some autoimmune issues. Late effects are usually defined as those that appear or persist 90 days after therapy. The most frequently observed delayed effect among late effects is hypogammaglobulinemia, a predictable OTOT consequence of CD19 targeted CAR T. In several key CD19 CAR T studies, reports indicated that the incidence of hypogammaglobulinemia varied between 44 to 83%. (10, 54-56) Patients who received BCMA-targeted CAR T cells have also exhibited prolonged depletion of immunoglobulins, which is also not unexpected considering that BCMA is expressed on healthy plasma cells as well, but since it is not expressed on B-cells earlier in the cell’s differentiation trajectory, this suggests that targeting BCMA is less likely to lead to hypogammaglobulinemia compared to targeting CD19. (57-59) It is important to note that the frequency of hypogammaglobulinemia varies among studies because it is influenced by various other factors, such as previous immunotherapies (e.g., rituximab) or pre-existing hypogammaglobulinemia. Hypogammaglobulinemia and prolonged cytopenias can elevate the susceptibility to late-emerging infectious complications. In a phase 1–2 clinical trial by Hill et al., 133 adult patients with relapsed or refractory CD19+ ALL, CLL, or NHL, received LD chemotherapy followed by CAR T. These patients, having an extensive treatment history, displayed significant immune compromise, evidenced by 26% having hypogammaglobulinemia and 12% neutropenia at baseline. Post-infusion, the infection incidence between 29 and 90 days was lower than that in the initial 28-day period. During this later phase, 23 infections (19 microbiologically confirmed) were recorded in 14% of patients, with viral infections being most prevalent (9%), followed by bacterial infections (6%). (60) Similarly, a study from the Fred Hutchinson Cancer Research Center assessed late infections following CD-19 directed CAR T in B-cell NHL and CLL patients and reported at least one infection in 61% of these patients, most frequently occurring in the respiratory tract. A vast 80% of these patients received treatment outside of hospital settings, with a mere 5% necessitating admission to the ICU. Bacterial agents were implicated in 60% of cases with identified causative organisms, followed by viral infections at 31%, and fungal infections accounting for 9%. (55)

**Long Term Effects**

Patient-reported outcomes (PROs), which consist of patients’ self-reported symptoms and functional status without external interpretation, play a crucial role in assessing novel therapies and enhancing patient care. PRO measures are now widely recognized as outcomes that supplement traditional survival endpoints. (61) These measures are instrumental in evaluating symptom burden, functional status and health-related quality of life (HRQoL) but there are also three somewhat new applications of PROs that include evaluating adverse events, research on comparative effectiveness, and quality assessment, also known as performance evaluation. (62) It has become evident that PROs provide a more accurate measure of treatment toxicity, or more accurately tolerability, than outcomes reported by clinicians and this is important also in the context of CAR T, especially in monitoring long-term consequences or in early phase trials. (63, 64) A variety of PRO measures exist but their abundance complicates comparisons across studies and populations. What is also obvious in CAR T-cell trials is that numerous investigators have concentrated on the prevalence of particular syndromes, yet often overlook the patient experience concerning isolated symptomatic manifestations. These symptoms may vary in persistence, occasionally being transient, yet at times they represent early indicators of potentially highly morbid syndromes, necessitating timely recognition. Consequently, there is a compelling need to focus greater attention on PROs and the experiential accounts of patients enduring IEC-related toxicities, as well as the potentially long-lasting repercussions of these therapeutic interventions.

Navigating the Selection of Domains and Instruments for Optimal Measurement of Patient-Reported Outcomes (PROs)

Numerous instruments exist for assessing PROs, typically falling into two main types: general and disease-specific measures. Widely utilized general measures encompass tools like the Medical Outcomes Trust Short-Form-36 (SF-36), Euro-QoL EQ-5D, and the Patient-Reported Outcomes Measurement Information System (PROMIS). In the realm of oncology, frequently employed cancer-specific measures in both research and clinical settings include the Functional Assessment of Cancer Therapy-General (FACT-G) and the EORTC-Quality of Life Questionnaire (EORTC-QLQ-C30). When designing a study involving patients undergoing CAR T cell therapy, the selection of PRO domains should be based on the specific disease and the therapy’s impact. For instance, different domains might be of importance in MM versus other B-cell malignancies. But as
we have previously emphasized, numerous factors related to the product and to the patient/disease influence the intensity of therapy toxicity, and ideally, all elements should be considered when constructing a study that also measures PROs. It has been proposed that researchers in cancer clinical trials, now extending to those encompassing CAR T, should focus on three specific measures of clearly defined concepts: symptomatic adverse events, physical function, and disease-specific symptoms. These elements are vital in determining how a therapy affects HRQoL. In 2014 The Symptom Management and HRQoL Steering Committee of the NCI defined a core set of 12 fundamental PRO-relevant symptoms to aid in designing cancer clinical trials. However, there’s a growing necessity to expand on the foundational research by Reeve and colleagues and the currently proposed core set of items to be used in cancer clinical trials. This expansion is essential not just in the context of CAR T but also in the broader spectrum of oncology, particularly in light of the increasing variety of new anticancer drugs, each with its distinct range of toxicities. Implementing a consistent core questionnaire for assessing PROs in individuals undergoing CAR-T is crucial to minimize variability and enable comparisons across different studies. The PROMIS, an initiative by the NIH, aims to standardize the measurement of common PROs in clinical research. Beyond general health surveys, PROMIS provides various item banks focused on key disease-related symptoms such as fatigue, neuropathy, dyspnea, and cognitive deficits, enabling the creation of tailored, hypothesis-specific instruments. An additional exciting and valuable resource for enhanced evaluation of treatment toxicity is the patient-reported outcomes version of the CTCAE (PRO-CTCAE). This tool encompasses about 10% of the items found in the CTCAE, featuring 78 symptomatic adverse events. Specific relevant adverse events can be selectively included in a study. However, an objective approach to item selection from a library is needed. The challenge is to identify a core list of common symptomatic toxicities aligned with modern treatment approaches such as CAR T, that can be used ad-hoc, and further research addressing this problem is ongoing from multiple stakeholders’ perspectives.

![Figure 1: Comparative overview of neuropsychiatric symptomatic adverse events (NP sAEs) associated with CAR T, aligned with the corresponding items from the PRO-CTCAE™ and the core symptoms set of the MDASI. The left section itemizes frequent NP sAEs, and the right section lists currently existing related PRO-CTCAE™ items alongside MDASI core symptoms and additional NP sAEs added in the new MDASI CAR Module.](https://example.com/image1)

Figure 1: Comparative overview of neuropsychiatric symptomatic adverse events (NP sAEs) associated with CAR T, aligned with the corresponding items from the PRO-CTCAE™ and the core symptoms set of the MDASI. The left section itemizes frequent NP sAEs, and the right section lists currently existing related PRO-CTCAE™ items alongside MDASI core symptoms and additional NP sAEs added in the new MDASI CAR Module. (69, 70)
Complexity of PRO evaluation in CAR T
The acute toxicities frequently manifesting post CAR T cell infusion, notably CRS and ICANS, present a formidable challenge in patient care due to their potential severity and profound impact on patient health and QoL. The task of capturing these side effects through PROs is rendered complex by the acute nature and intricacies of these symptoms. Patients in critical condition, grappling with these adverse effects, may find it difficult to self-report their experiences, particularly when facing cognitive impairments or intense physical discomfort that impede effective communication. A crucial aspect to consider is the temporal variation of these symptoms; the emergence and evolution of side effects such as CRS and ICANS can differ, ranging from immediate post-infusion reactions to delayed onset of weeks. This necessitates an adaptable and dynamic methodology in PRO assessment to precisely monitor these fluctuations over time. Considering the critical nature of these side effects, integrating PRO data collection with clinical care is paramount for ensuring patient safety and reducing data collection burdens. Employing a flexible, and possibly daily, approach in gathering PRO data, such as utilizing PRO-CTCAE right after CAR T cell infusion, offers a strategic advantage. It could also enable healthcare providers to rapidly receive alerts about any worsening of symptoms, thereby facilitating more immediate and effective medical interventions. When focusing on long-term effects of CAR T, capturing those is a complex task, given the unique characteristics of this treatment and the diseases it targets. This process extends well beyond the scope of traditional therapies, necessitating a prolonged period of follow-up to fully understand the long-term outcomes, with an emphasis on neurological consequences. The importance of tracking these effects lies in providing comprehensive patient care and gaining a deeper understanding of the therapy’s full impact. A significant aspect of long-term monitoring is the assessment of HRQoL, influenced both by the therapy and underlying disease. Utilizing PRO measures is essential in both contexts, as they offer insights into the patient perspective on their health and the effects of the treatment over time. The effectiveness of long-term monitoring relies heavily on robust data collection and management systems. The employment of electronic health records (EHRs), electronic patient-reported outcomes (ePROs), and telemedicine could be a key in facilitating this process, ensuring that the long-term effects of CAR T are captured accurately and comprehensively.

PROs in CAR T Clinical Trials
Despite existing research, there remains a notable scarcity of published data on the use of PROs in CAR T context. A panel from the Centers for Medicare & Medicaid Services (CMS) endorsed the effectiveness of four validated measurement tools: PRO-CTCAE, MD Anderson Symptom Inventory (MDASI), EORTC-QLQ-C30, and PROMIS. This endorsement reflects a scientific consensus on the reliability and validity of these instruments in assessing PROs in the CAR T clinical setting. (71) The scoping review by Efficace et al. on PROs in CAR T cell therapy for hematologic malignancies identified 14 studies that included PRO measures important for understanding the patient perspective on the impact of CAR T cell therapy. The EQ-5D and PROMIS-29 were the most frequently used PRO measures and were employed in 6 (42.9%) and 5 (35.7%) of these studies, respectively. The authors emphasized the importance of longitudinal monitoring of patient experiences in order to learn more about the tolerability of this new therapy. (72) The integration of PROs in early-phase clinical trials, particularly within advanced cancer cohorts, represents a challenge, yet, emerging evidence robustly underscores the viability of PRO assessment in these contexts, revealing its capacity to generate data that is not only clinically relevant but also of good quality. (Table 1) The ELIANA and JULIET studies assessed tisa-cel’s impact on HRQoL in pediatric/young adult patients with R/R B-ALL and adult patients with R/R DLBCL, respectively. In ELIANA significant and ongoing HRQoL improvements post-tisa-cel infusion, using PedsQL and EQ-5D VAS were observed, with reduced benefits in patients with severe CRS or neurotoxicity. Conversely, JULIET study reported substantial, enduring HRQoL enhancements in adult DLBCL patients, measured by FACT-Lym and SF-36. The ZUMA-2 and ZUMA-3 studies evaluated the impact of brexucel on HRQoL in adults with R/R MCL and ALL, respectively. Wang et al. observed in R/R MCL patients a temporary HRQoL decline at week 4 post-brexucel infusion, with a subsequent return or improvement at 3 and 6 months, as measured by EQ-5D scores. Shah et al. found that most evaluable adult R/R ALL patients experienced stable or improved HRQoL over time post-infusion, with a notable increase from the third month. In the KarMMa study, patients with triple-class exposed R/R MM receiving ide-cel as fourth-line or later treatment reported significant improvements in most PROs by the first month, including pain and disease symptoms. These enhancements, covering aspects like fatigue, physical and cognitive functioning, HRQoL, and disease symptoms, were sustained from the second through the ninth month, as measured by the EORTC QLQ-C30 and QLQ-MY20. Moreover, patients’ baseline HRQoL scores, initially worse than the general population, aligned with or exceeded those of the general population from one to three months and persisted through the eighteenth month. (56, 73-76) The Efficace et al. research unveiled an important gap: only a few studies have delved into data on PROs in the two-week window post CAR T-cell infusion and the critical long-term phase, surpassing the one-year mark. This paucity stands in stark contrast to existing research underscoring the criticality of longitudinal PRO data to unearth latent symptoms or functional impairments that might only surface months, if not years, after therapy. This illuminates a significant frontier awaiting further exploration.
<table>
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<th>Product Name</th>
<th>FDA Approval for Current Indications</th>
<th>Reference</th>
<th>Indication</th>
<th>No. of Evaluable Patients</th>
<th>CRS</th>
<th>Neurological Events/Neurotoxicities</th>
<th>CRS Grading</th>
<th>Neurotoxicity Grading</th>
<th>PRO Instruments</th>
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<td>Tisagenlecleucel</td>
<td>2017</td>
<td>(10)</td>
<td>Patients up to 25 years of age with B-ALL that is refractory or in second or later relapse</td>
<td>75</td>
<td>77%</td>
<td>40%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Penn/CHOP scale</td>
<td>NCI CTCAE v4.03</td>
<td>PedsQL and EQ-5D, EQ-VAS</td>
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<td>2017</td>
<td>(28)</td>
<td>Adult patients with R/R LBCL after 2 or more lines of systemic therapy, including DLBCL, NOS, PMBL, high grade B-cell lymphoma and DLBCL arising from FL</td>
<td>108</td>
<td>93%</td>
<td>64%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03</td>
<td>EQ-5D, MMSE</td>
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<td>Tisagenlecleucel</td>
<td>2018</td>
<td>(78)</td>
<td>Adult patients with R/R LBCL after 2 or more lines of systemic therapy, including DLBCL, NOS, high grade B-cell lymphoma and DLBCL arising from FL</td>
<td>93</td>
<td>58%</td>
<td>21%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Penn scale</td>
<td>NCI CTCAE v4.03</td>
<td>FACT-Lym and SF-36</td>
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<td>Brexucabtagene Autoleucel</td>
<td>2020</td>
<td>(81)</td>
<td>Adult patients with R/R MCL</td>
<td>68</td>
<td>91%</td>
<td>63%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03</td>
<td>EQ-5D and VAS score</td>
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<td>Lisocabtagene Maraleucel</td>
<td>2021</td>
<td>(80)</td>
<td>Adult patients with LBCL, DLBCL, NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, PMBL, and FL grade 3B with refractory disease to first-line chemoimmunotherapy or relapse within 12 months, or who are not eligible for HSCT or with R/R disease after 2 or more lines of systemic therapy</td>
<td>269</td>
<td>42%</td>
<td>30%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 1. FDA-approved CAR T cell therapies – Prevalent Toxicity and PROs used.
<table>
<thead>
<tr>
<th>Product Name</th>
<th>FDA Approval for Current Indications</th>
<th>Reference Indication</th>
<th>No. of Evaluable Patients</th>
<th>Neurotoxicity Grading</th>
<th>CRS Grading</th>
<th>PRO Instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axicabtagene Ciloleucel</td>
<td>Adult patients with R/R FL after 2 or more lines of systemic therapy (77)</td>
<td>CRS Neurological Events/Neurotoxicity</td>
<td>148 82% 59%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>EORTC-QLQ-C30, EQ-5D-5L, EORTC-QLQ-MY20</td>
</tr>
<tr>
<td>Idecabtagene Vicleucel</td>
<td>Adult patients with R/R MM after 4 or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (83)</td>
<td>CRS Neurological Events/Neurotoxicity</td>
<td>128 84% 18%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03 and ASTCT consensus grading</td>
</tr>
<tr>
<td>Cilcarabagene Autoleucel</td>
<td>Adult patients with R/R MM after 4 or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody (82)</td>
<td>CRS Neurological Events/Neurotoxicity</td>
<td>97 95% 21%</td>
<td>NCI CTCAE v5.0 (specific symptoms) and ASTCT consensus grading</td>
<td>NCI CTCAE v5.0 and ASTCT consensus grading</td>
<td>NCI CTCAE v4.03, SF-36v2, FACT-Lym, EQ-5D-3L, PGIC, PGIS, single items from EORTC QLQ-MY20</td>
</tr>
<tr>
<td>Tisagenlecleucel</td>
<td>Adult patients with R/R FL after 2 or more lines of systemic therapy (79)</td>
<td>CRS Neurological Events/Neurotoxicity</td>
<td>97 47% 36%</td>
<td>NCI CTCAE v4.03 (specific symptoms) and Lee scale</td>
<td>NCI CTCAE v4.03 and ASTCT ICANS consensus grading</td>
<td>SF-36v2, FACT-Lym, EQ-5D-3L</td>
</tr>
</tbody>
</table>

Table 1. FDA-approved CAR T cell therapies – Prevalent Toxicity and PROs used.
In the dynamic landscape of CAR T, the systematic tracking of PROs emerges as a pivotal tool, particularly for capturing the nuances of late-onset toxicities, such as neurocognitive deficits, thus charting new territories in patient-centric medical research. Up to now, to our knowledge, only one PRO instrument has been developed specifically for patients treated with CAR T. Wang et al. conducted a cross-sectional study with the goal of creating and validating a PRO tool specifically designed to measure symptom burden and daily functioning in patients who have undergone CAR T-cell therapy. This instrument, MDASI-CAR, is an extension of the established MDASI. The MDASI-CAR represents a pioneering effort in developing a treatment-specific PRO assessment tool for CAR T patients. The research led to the identification and inclusion of 10 critical symptoms – tremors, fever/chills, headaches, balance problems, dizziness, attention issues, speech difficulties, coughing, sexual dysfunction, and diarrhea – into the existing MDASI framework, forming the final version of the MDASI-CAR instrument. (70)

**Conclusion**

CAR T represents a significant advancement in treatment of hematological malignancies, introducing a range of unique adverse events whose frequency and severity vary considerably. The complexity of understanding and managing this therapy’s toxicities constitutes a serious challenge in the medical field. A deeper insight into the pathophysiology of these side effects is also crucial, demanding an effort in both basic and clinical research. This research is vital to determine why certain patients experience specific side effects and it would help in prevention, earlier recognition, and treatment of these side effects. Moreover, the diverse symptomatology associated with individual CAR-T syndromes, each with its own frequency, requires more precise characterization. It underscores the need for a systematic approach to patient care, emphasizing the importance of directly understanding patients’ experiences with these side effects. To this end, the consistent application of PRO instruments across clinical studies is essential. Healthcare professionals continue to search for an optimal PRO tool capable of identifying early and late-stage toxicities. It is crucial to closely monitor PROs shortly after therapy to gather information on acute toxicity. This monitoring enables timely interventions to reduce symptom severity and potentially prevent the escalation of CRS and ICANS to more severe grades. Assessing PROs at later stages is equally vital for evaluating long-term QoL, particularly in relation to neurocognitive effects.

Current PRO tools, most not originally tailored for CAR T-cell therapy, highlight a significant gap in our research methodologies, necessitating further exploration to establish a core set of symptoms, following on Reeve’s set. Such a set would be valuable in tracking patient experiences in clinical trials and would provide important and needed information on the tolerability of the therapy as well as enable comparisons of different CAR T products with similar response rates.

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References


51. Teachey DT, Bishop MR, Maloney DG, Grupp SA. Toxicity management after chimeric antigen receptor T cell


