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Patient-Reported Outcomes with Chimeric Antigen Receptor T Cell Therapy: Challenges and Opportunities

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A B S T R A C T

Patient-reported outcomes (PROs) are an important tool to assess the impact of a new therapy on symptom burden and health-related quality of life (HRQoL). Chimeric antigen receptor T (CAR-T) cell therapies have been approved for use in relapsed or refractory leukemia and lymphoma based on promising efficacy in clinical trials. However, data are lacking on patient-reported toxicity and impact on HRQoL. This review provides an overview of the incorporation of PROs in CAR-T cell therapy and the specific challenges in this context. The first step is to demonstrate feasibility of PRO monitoring in the acute phase after CAR-T cell infusion. Apart from core PRO domains like physical functioning, disease-related symptoms, and symptomatic adverse effects, important measures to consider are cognitive functioning and financial toxicity. Because there are no validated PRO instruments in the setting of CAR-T cell therapy, universally validated measures like Patient-Reported Outcomes Measurement Information System (PROMIS) could be considered, which is also recommended in the setting of hematopoietic stem cell transplantation. Given the timeline of toxicities with CAR-T cell therapy, PRO instruments should be administered at baseline and at least weekly in the first 30 days. Subsequently, frequent monitoring of PROs in the first year might be helpful in identifying short- and intermediate-term toxicities, functional limitations, and neuropsychiatric effects. The major potential challenge in acute phase would be missing data when patients develop severe cytokine release syndrome or neurotoxicity. Designing a strategy for handling missing data is crucial. The long-term safety of CAR-T cell therapy is not well characterized because of short follow-up in most studies reported thus far. PROs should be measured at least yearly after the first year to identify potential late effects like cognitive deficit or autoimmune manifestations. Collaboration between institutions performing cellular therapy and engagement with patients, clinicians, and statisticians with expertise in PROs are crucial for setting a comprehensive agenda on integration of PROs with CAR-T cell therapy.

INTRODUCTION

The development of chimeric antigen receptor T (CAR-T) cell therapy has revolutionized the treatment of relapsed and refractory malignancies. The US Food and Drug Administration (FDA) has approved CD-19 CAR-T cell therapy for treatment of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) and diffuse large B cell lymphoma based on impressive response rates in registration studies [1,2]. Several clinical trials on CAR-T cells are currently ongoing in multiple hematologic and solid malignancies, and the common toxicities associated with this therapy have been well described. However, as clinical trials on CAR-T cells continue to mature with further data on durability of remission and long-term toxicity, it is also critical to measure the patients' perspective on symptom burden and overall well-being. Patient-reported outcomes (PROs) are a method of measuring health status by information obtained directly from the patient without clinician interpretation. PROs can be used to assess symptom burden, health-related quality of life (HRQoL), comparative effectiveness of treatment strategies, and quality of care [3]. From prior experience in solid tumors and hematopoietic stem cell transplantation (HSCT), we have learned that PROs are a better indicator of treatment toxicity compared with clinician-reported outcomes [4-8]. Furthermore, multiple randomized controlled trials have demonstrated that systematic surveillance of PROs during cancer therapy leads to improved HRQoL and overall survival (OS) [9,10]. Information obtained from PROs is highly valued by patients and physicians alike and leads to increased engagement of patients with the healthcare team [11].

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CAR-T cell therapy is associated with a unique toxicity profile due to activation of the immune system after infusion of engineered T cells. Although we have a fair amount of data on the acute toxicities of CAR-T cell therapy, like cytokine release syndrome (CRS) and CAR-T related encephalopathy syndrome (CRES), certain critical questions from the patients' perspective remain unanswered: When do patients experience peak symptom burden and how does the trajectory of symptoms look like after CAR-T cell infusion? When can patients expect their physical functioning to return to baseline? What is the impact of therapy on psychosocial health and functioning? Are there any potential long-term effects of therapy? Without rigorously incorporating PRO assessment, we risk missing patients' perspective of toxicity and efficacy with this new treatment modality. In addition, the FDA now recognizes PROs as a measure of clinical benefit when pharmaceutical companies seek approval for their products. In the era of value-based medicine, the concept of "clinically meaningful benefit" will be held to higher standards, including demonstration of improvement in PROs in addition to traditional outcomes like response rate, progression-free survival, and OS.

In this review we outline an agenda for incorporation of PROs in different phases of CAR-T cell therapy, propose the time points for measurement of PROs after CAR T-cell therapy (Figure 1), and identify the challenges of routinely incorporating PRO measures specific to this therapy.

PHASES OF THERAPY

Preinfusion Phase

The preinfusion phase of CAR-T cell therapy consists of optimal patient selection, successful cell manufacturing, and administration of lymphodepleting chemotherapy. Currently, most patients arrive to CAR-T cell therapy with relapsed or refractory disease after exhausting multiple lines of treatment. Patients may have existing deficits in multiple dimensions of HRQoL like physical and social functioning because of the disease itself and cumulative toxicity of prior therapies. Furthermore, the long-term implications of therapy, as to whether CAR-T cells will be curative, a bridge to definitive treatment like HSCT in certain malignancies, or only provide durable disease control, is not known at present [12]. This can potentially generate anxiety and distress among patients and caregivers.

Two large meta-analyses in solid tumors have shown that baseline PROs are important predictors of OS [13,14]. The most common PROs that predicted for OS in these studies were global QoL, physical functioning, and specific symptoms like appetite loss, fatigue, and pain. In a meta-analysis by Quinten et al. [14] that included individual patient data from 30 European Organization for Research and Treatment of Cancer (EORTC) clinical trials, baseline PRO and *not* clinician-reported performance status was a significant predictor of OS in multivariable analysis. In the setting of HSCT, pretransplant PROs are known to be associated with post-transplant outcomes [15-18]. Poor patient-reported physical functioning before HSCT and decline in physical functioning early after HSCT are associated with a higher overall mortality [18]. Pretransplant depression is also associated with lower OS, higher incidence of acute graft-versus-host-disease (aGVHD), and increased duration of hospitalization in the first 100 days after HSCT [19]. Furthermore, baseline PROs are valuable for longitudinal analysis of HRQoL trajectory and identification of meaningful benefit or harm from treatment. A meta-analysis by Victorson et al. [20] showed that improvement in PRO with therapy correlated well with radiographic complete or partial response in solid tumors. However, the duration of PRO response was found to be shorter than that of radiographic response, which implies that change in PROs with time might be a more sensitive indicator of disease progression.

Based on available literature in other malignancies and treatment settings, baseline PROs should be routinely captured in patients undergoing CAR-T cell therapy. The objective would be to identify targetable deficits in HRQoL, such as high psychosocial distress, poor physical functioning, or high symptom burden. Furthermore, as data mature, specific PRO measures that are most sensitive to change over time can be identified for development of novel patient-centered endpoints. Early symptoms might also be predictive for impending CRS or CRES. The impact of baseline PRO on OS and post-treatment HRQoL can also be assessed in future studies.

Acute Phase

The acute toxicities commonly observed after CAR-T cell infusion includes CRS and CRES. CRS is the most common toxicity with incidence of all-grade events ranging from 57% to 93% and grade 3 or higher events from 13% to 32% in current trials [2,21-24]. The most common symptoms of CRS include pyrexia, hypotension, and hypoxia [25]. In clinical trials thus far the median time from infusion of CAR-T cells to development of CRS has been around 2 to 4 days, with the duration of CRS being 5 to 6 days [2,21]. Tocilizumab, a humanized monoclonal antibody against IL-6 receptor, is a preferred therapy for the treatment of CRS, apart from supportive care [25]. In a clinical trial testing tocilizumab before allogeneic SCT for aGVHD prophylaxis, patients were found to have significantly worse anxiety, depression, pain, and sleep compared with historical control subjects in the short term after transplantation [26].

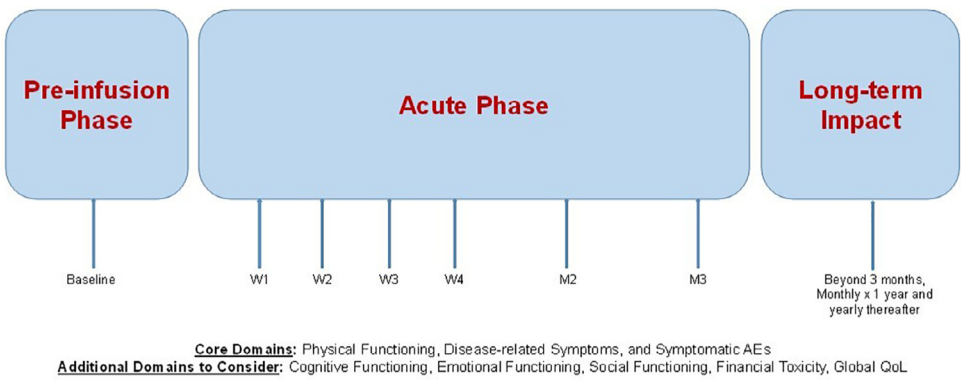

Figure 1. Potential time points for measurement of PROs with CAR-T cell therapy.

Neurologic toxicity or CRES typically manifests as decreased attention span, language disturbance, and impaired handwriting. It can also have potentially severe manifestations including obtundation, seizures, and cerebral edema [25,27]. The incidence of all-grade and at least grade 3 CRES has ranged from 29% to 64% and 11% to 42%, respectively, in clinical trials thus far [2,21-24]. CRES can manifest within 5 days of infusion concurrently with CRS or can be delayed in some cases, typically after CRS has resolved [25]. The CAR-T-cell Therapy Associated Toxicity (CARTOX) working group recommends hospitalization for a period of at least 7 days after infusion to monitor closely for potentially severe toxicities. Most clinical trials in CAR-T cell therapies thus far have mandated a minimum duration of hospitalization. In the CAR-T cell study on chronic lymphocytic leukemia, the median duration of hospitalization was 9 days (range, 0 to 49) [24]. Data on real-world incidence of acute toxicities and duration of hospitalization with the use of FDA-approved CAR-T cell therapies will provide a better understanding of tolerability.

Although the timeline and biology of toxicity is different, the overall trajectory of acute toxicity after CAR-T cell infusion resembles that of HSCT. Monitoring of patient-reported symptoms and HRQoL is feasible in the acute setting of first 100 days after HSCT, with compliance rates of more than 90% [28]. Furthermore, toxicities like aGVHD after HSCT can lead to a durable decline in HRQoL [29], which highlights the importance of measuring patients' perspective to identify important determinants of QoL. Blinatumomab, a bispecific monoclonal antibody that activates T cells, is also known to cause CRS in 2% to 5% of patients with relapsed or refractory B-ALL [30,31]. In the phase III TOWER study comparing blinatumomab with chemotherapy in heavily pretreated B-ALL, baseline and at least 1 postbaseline HRQoL measurement were completed by 91% of patients, which demonstrates the feasibility of obtaining PROs in this patient population receiving immunotherapy [32]. In patients receiving CAR-T cell therapy, to the best of our knowledge, there are no published data on feasibility of PRO monitoring in the acute phase. Hence, longitudinal studies on PRO monitoring in the acute phase of CAR-T cell infusion should be conducted to demonstrate feasibility and identify important symptoms or concerns that are bothersome to patients and affect their HRQoL. Furthermore, it will help in comprehensive evaluation of neuropsychiatric manifestations from the use of IL-6 antagonists and corticosteroids in the acute phase. The biology of IL-6 receptor modulation and impact on physical and mental health is complex [33], and valuable insights could be gained by incorporating patients' direct input. PRO measurement should be done at least once a week in the acute phase. However, to potentially predict impending CRS or CRES, PROs could be monitored more frequently, like daily or every other day in the acute phase after CAR-T infusion. Pilot studies on PROs as a clinical trigger for comprehensive toxicity assessment should be done to explore this hypothesis. This might be particularly important in the context of outpatient CAR-T cell infusion and monitoring, which is being done with certain CAR constructs like 4-1BB [34]. One of the potential challenges in the acute phase of CAR-T cell therapy is missing data in periods when patients develop encephalopathy or severe CRS. This is discussed in more detail below in Challenges.

The toxicity profile of CAR-T cells in the context of solid tumors might be different from that in hematologic malignancies. The engraftment and proliferation of CAR-T cells in solid tumors have been found to be low compared with that in leukemia, resulting in low incidence of "on-target on-tumor" toxicities like CRS [35,36]. However, fatal "on-target off-tumor" toxicity has been noted in solid tumors, for example, severe pulmonary toxicity with ERBB2 CARs noted in a patient with metastatic colon cancer [37]. Hence, the trajectory of toxicities and potential time points for measurement of PROs in the context of solid tumors remain unclear as of yet.

Financial burden because of the high cost of CAR-T cell therapy can potentially lead to increased emotional distress and maladaptive coping, which can adversely affect health outcomes [38,39]. The price of the CAR-T product ranges from $373,000 to $475,000 for currently approved agents. This, however, does not account for additional procedures including lymphodepleting chemotherapy, leukapheresis, management of toxicities like CRS, and frequent follow-up visits after hospital discharge. A cost-analysis study has shown that the nondrug cost in patients with CRS is approximately $56,000 higher compared with those without CRS. Furthermore, the proposed outcomes-based pricing arrangement of CAR-T cell therapy does not reimburse the nondrug cost in situations where therapy fails to induce a response [40]. The out-of-pocket expenditure for patients might vary depending on their insurance coverage. Hence, screening for financial toxicity could be done using PRO instruments like COST, or COmprehensive Score for financial Toxicity [41]. It can initiate a conversation between patients and clinicians and facilitate referral to social worker or care navigators who are generally better equipped in handling financial burden issues [39]. In the long run it can also provide valuable data to negotiate reimbursement issues with payers including private insurance companies and Centers for Medicare & Medicaid Services.

The toxicity of treatment, both physical and financial, also impacts caregivers in addition to patients. Caregiver well-being should be taken into consideration while evaluating the outcomes of CAR-T cell therapy. In the setting of HSCT, a large study on more than 800 caregiver–recipient pairs has shown that 1 in 5 caregivers has poor QoL compared with the general population norm. Furthermore, the incidence of depression and sleep disorders was more common in caregivers compared with the general population [42]. Studies measuring PROs in caregivers of CAR-T cell recipients, especially in the acute phase when major toxicities are anticipated, are needed to better identify specific caregiver populations that might benefit from interventions directed to improve QoL.

Long-Term Impact

Based on available data thus far, it is unclear whether CAR-T cell therapies will be potentially curative in some cancers or a bridge to a more definitive therapy like HSCT [12]. One of the longest follow-ups reported thus far has been from the Memorial Sloan Kettering Cancer Center group on the efficacy and toxicity of 19-28z CAR-T cells in relapsed B-ALL [22]. At a median follow-up of 29 months the median event-free survival and OS in this trial was 6 and 13 months, respectively. Although patients who achieved minimal residual disease negativity had a superior event-free survival and OS, 50% with minimal residual disease– negative complete response have already experienced relapse. With data on longer follow-up in large cohorts, we will have precise estimates of the likelihood of relapse over time and optimal postremission therapeutic strategies in the context of different malignancies. Based on the meta-analysis by Victorson et al. [20], which showed that change in PROs might be a sensitive indicator of disease relapse, longitudinal monitoring of PROs after CAR-T cell therapy might help improve outcomes by earlier detection of

relapse when patients are in a better performance status and eligible for intensive therapies.

Potential long-term concerns after CAR-T cell therapy include increased risk of infection due to B cell aplasia with CD-19 CARs or plasma cell aplasia with B cell maturation antigen CARs, residual cognitive deficit in patients experiencing CRES, emergence of new or exacerbation of existing autoimmune toxicities, and development of recurrent or second primary malignancies. Furthermore, PROs might be a sensitive tool to capture potential change in disease-related symptoms after CAR-T cell therapy. Older adults might be at a higher risk of cognitive dysfunction, which is clinically relevant in certain patient populations like multiple myeloma, with a median age at diagnosis of 69 years [43]. Another important concern for patients is return to work after therapy. Studies in the HSCT setting have shown that 30% to 60% of patients return to work by 1 year post-transplant [44,45]. Similar data in the context of CAR-T therapy will be informative for patients, especially with comparative effectiveness studies of CAR-T versus autologous HSCT already underway in relapsed non-Hodgkin lymphoma. Data on long-term neuropsychiatric manifestations and emotional sequelae of CAR-T cell therapy and associated toxicities by consistent and standardized PRO measurement will also be valuable for survivorship care in this patient population.

The duration of PRO monitoring after CAR-T cell therapy to identify its long-term impact is not yet defined and will partly depend on the goal and outcome of therapy. For example, if it proves to be curative in a situation, long-term PRO monitoring to identify late effects will be important. On the other hand, if the intent of treatment is to delay progression and patients receive multiple lines of therapy after CAR-T cells, data on long-term PRO measures will be contaminated by toxicity of other treatments. For example, preliminary results from bb121 CAR-T cell therapy in multiple myeloma showed a median progression-free survival of 11.8 months [46], which implies a large number of patients will subsequently receive nontransplant novel agents at relapse. Important aspects to consider while interpreting long-term PRO data are subsequent therapies (which might include HSCT), disease status, and response shift.

SPECIFIC CHALLENGES IN THE CONTEXT OF CAR-T CELL THERAPY

How to Select the Domains and Instruments to Measure PROs?

Successful PRO measurement provides maximal information about patients' health status with a minimal burden to patients and caregivers. Electronic PRO monitoring is feasible and has been implemented at many institutions and healthcare systems. Integration of electronic PRO with electronic medical records can provide easy access to clinicians and generate research quality data [47,48].

The PRO domains of interest while designing a study in patients receiving CAR-T cell therapy will depend on the disease and impact of therapy. For example, in patients with multiple myeloma bone pain, neuropathy, and fatigue might be important determinants of HRQoL and should be followed longitudinally to assess the impact of therapy on these symptoms. Furthermore, the toxicity profile can vary depending on the CAR construct, preinfusion disease burden, CAR-T cell dose, lymphodepleting chemotherapy, and use of bulk $CD8^+$ T cell selection [25,34,49]. The core PRO domains that are important contributors to HRQoL and can be measured with contemporary instruments include physical functioning, disease-related symptoms, and symptomatic adverse events (AEs) [50]. The National Cancer Institute's Symptom Management and HRQoL steering committee has outlined a set of 12 core PRO-relevant symptoms, which can serve as a guide for inclusion in clinical trials [51].

A wide variety of instruments are designed for measuring PROs, which can be broadly classified into 2 categories: universal and disease-specific measures. Universal measures are typically designed in a large population of patients with a variety of chronic conditions. Commonly used universal measures include Medical Outcomes Trust Short-Form-36 (SF-36), Euro-QoL EQ-5 dimensions (EQ-5D), and Patient-Reported Outcomes Measurement Information System (PROMIS). SF-36 is a 36-item survey containing several domains, including physical functioning, role functioning, bodily pain, general health perceptions, vitality, social functioning, and general mental health. It generates physical and mental component summary scores, which can be compared with normative scores for general population [52]. EQ-5D is a generic questionnaire used to measure overall health status and contains 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) [53]. It is a standardized instrument for measuring generic health status and has been widely used for cost-utility analysis. The PROMIS questionnaires have been developed using advanced qualitative and quantitative methods and validated in multiple chronic conditions including cancer [54-57]. Apart from global health questionnaires, PROMIS offers several item banks on important disease-related symptoms like fatigue, neuropathy, dyspnea, and cognitive deficit, which can be used to generate customizable hypothesis-driven instruments. Cancer-specific measures commonly used in research and clinical practice include Functional assessment of Cancer Therapy-General (FACT-G) and EORTC-Quality of Life Questionnaire (EORTC-QLQ-C30). The EORTC QLQ-C30 questionnaire includes 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), a global health/QoL scale, and 6 single items for common chemotherapy-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) [58]. FACT-G contains 27 questions divided into 4 core subscales: physical well-being, social well-being, emotional well-being, and functional well-being [59]. Even among cancer-specific instruments like FACT-G and EORTC-QLQ-C30, there are differences in scale domains, scale structure, and concept or tone of specific measures. For example, the social well-being domain of FACT-G focuses on social support and relationships, whereas the social functioning domain of EORTC-QLQ-C30 focuses more on the impact of therapy on social activities [60].

Currently ongoing clinical trials in CAR-T cell therapy (Table 1) use both cancer-specific instruments like EORTC-QLQ-C30 and universal instruments like PROMIS and Euro-QoL EQ-5D. Furthermore, the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is also being used for toxicity assessment in certain studies. Clinical trials on CAR-T cells are currently measuring PROs up to 15 years from infusion. An optimal PRO instrument should be valid, reliable, responsive to change, and generalizable to the target patient population [50,61]. Furthermore, from a pragmatic standpoint, ease of interpretation of PRO data generated by the desired instrument is critical for increased uptake by clinicians. The use of a similar core questionnaire for measuring PROs in patients receiving CAR-T therapy is important to reduce heterogeneity and facilitate cross-study comparison. In the setting of HSCT the Center for International Blood and Marrow Transplant Research recommends using PROMIS as a core questionnaire in future studies because of its high correlation with

Table I
List of Currently Ongoing Clinical Trials in CAR-T Cell Therapy with PROs as an Endpoint

Clinicaltrials.gov Identification Nos.	Disease	PRO Instrument (Measures and Domains)	PRO Administration Time Point
NCT03086954	CD-19 positive lymphoma	EORTC quality of life of the core scale criteria QLQ-C30 (V3.0)	Time frame: 3 years
NCT03144583	CD-19+ leukemia or lymphoma	Not provided	Time frame: months 3, 6, 12
NCT02919046	Neuroblastoma	EORTC quality of life measurement scale PedsQL4.0 children's quality of life of the core scale of the evaluation and comparison of physical condition before and after treatment	Time frame: 3 years
NCT03355859	B cell NHL	Not provided	Time frame: 2 years
NCT03030001	Mesothelin-positive advanced malignancies	Not provided	Time frame: 6 months
NCT02690545	$CD30^{+}$ HL and NHL	NCI PRO-CTCAE, PROMIS GHS SF v1.0-1.1 (10-item), PROMIS Physical Function SF20a	At baseline and over time
NCT03361748	Multiple myeloma	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L, and EORTC-QLQ-MY20	Time frame: minimum of 24 months postinfusion
NCT03207178	B cell lymphoma	Not provided (Domains: Appetite, Sleep, Pain and Mental State)	Time frame: 1 year
NCT03179007	MUC1-positive advanced solid tumors	Not provided	Time frame: 2 years
NCT03182816	EGFR-positive advanced solid tumors	EORTC-QLQ-C30	Time frame: 2 years
NCT03182803	Mesothelin-positive advanced solid tumors	EORTC-QLQ-C30	Time frame: 2 years
NCT02208362	Malignant glioma	EORTC-QLQ-C30 and EORTC-QLQ-BN20	Time frame: 15 years (estimate the mean and standard error for change from baseline during treatment and post-treatment in the quality of life functioning scale, symptom scale, and item scores from the EORTC QLQ-C30 and the domain scale and items scores from the QLQ-BN20)
NCT03484702	Aggressive B cell NHL	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L, and FACT-Lym	Time frame: 2 years
NCT03016377	ALL	NCI PRO-CTCAE, PROMIS GHS SF v1.0-1.1 (10-item), PROMIS Physical Function SF20a	Time frame: 15 years
NCT03310619	B cell malignancies	EORTC-QLQ-C30 and Euro-QoL-EQ-5D-5L	Time frame: 2 years
NCT03331198	CLL/SLL	EORTC-QLQ-C30, Euro-QoL-EQ-5D-5L and QLQ-CLL	Time frame: 2 years
NCT03483103	Aggressive B cell NHL	EORTC-QLQ-C30 and Euro-QoL-EQ-5D-5L	Time frame: 2 years

QLQ-C indicates Quality of Life Questionnaire-Cancer; NCI, National Cancer Institute GHS, Global Health Survey; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; ALL, acute lymphoblastic leukemia; EGFR, epidermal growth factor receptor.

traditional measures like SF-36, ease of comparison with the general population, and free availability [62,63]. PROMIS-29 can be used as a global profile because it covers important dimensions of HRQoL including physical function, fatigue, anxiety, depression, pain, social well-being and sleep. Furthermore, PROMIS measures also have computerized adaptive testing that can generate dynamic questionnaires accommodating a broad range of patient functioning. On the other hand, cancer-specific measures like FACT might have some advantages including availability of historical data in different cancer subtypes for comparison and tumor-specific supplements like FACT-MM that can added to the core questionnaire depending on the context. Another important tool that could be incorporated for better assessment of treatment toxicity is the PRO-CTCAE [64]. PRO-CTCAE contains approximately 10% of items included in CTCAE, including 78 symptomatic adverse effects. Relevant adverse effects can be selected individually for inclusion in a study. The use of PRO-CTCAE to generate mean symptom scores in the acute phase of HSCT is feasible with a high compliance rate [28], which lays the groundwork for its use in the acute phase of CAR-T cell therapy. If this tool is used, an important question going forward is which of the 78 toxicities to include to minimize patient burden while still gathering important AEs. Data from clinical trials describing physician-reported AEs and pilot studies of patient-reported AEs may provide direction.

The development of an ideal PRO measure that is psychometrically robust and clinically relevant consumes time and resource. With availability of universal measurement systems like PROMIS and PRO-CTCAE, which have been adequately validated in cancer population, investigators can develop customized instruments to assess feasibility of PRO monitoring in the context of CAR-T cell therapy. Given the uniqueness of its toxicity profile, the specific things we want to measure may not be incorporated in just 1 scale. Hence, the choice of item banks should depend on the hypothesis of a study. Pilot studies to establish feasibility along with input from key stakeholders including patients are urgently needed for standardization of PRO measurement in future clinical trials of CAR-T cell therapy.

How to Handle Missing Data?

Missing data can impose a statistical challenge in interpretation of PROs and introduce bias if the amount of missing data

is substantial. The PRO extension of the Consolidated Standards of Reporting Trials requires the statistical approaches for dealing with missing data to be categorically mentioned in the study protocol [65]. In patients receiving CAR-T cell therapy, it is expected that at least one-third will develop severe CRS or CRES, which might compromise their ability to complete PRO instruments at certain time points in the acute phase. Furthermore, at present, patients are mostly traveling to referral centers for CAR-T cell therapy, where they are typically followed in the acute phase, followed by transition of care to local oncologists. This can result in generation of missing data in the long-term. The statistical methods to handle missing data have been reviewed elsewhere [66] and are beyond the scope of this review. Investigators should consider the following pragmatic issues while designing their PRO study in patients receiving CAR-T cell therapy. First, it is important to avoid generation of significant missing data by training study personnel, monitoring data compliance in real-time, and designing a thoughtful PRO assessment schedule. Second, it is critical to capture auxiliary data to supplement PRO data at missing time points. In the acute phase of therapy assessment and grading of CRS by 1 of the grading algorithms and neurologic assessment by CARTOX-10 should be performed at regular intervals [25]. Because clinician-reported toxicity might be strongly related to the missing data mechanism and outcome, it can function as a proxy for PRO in the appropriate context. It can also be used for multiple imputation and sensitivity analysis. A systematic review on caregiver or proxy responses in adult cancer care has shown mixed results, with clinically important variability [67]. Hence, the role of proxy PRO response from caregivers in the setting of severe toxicity precluding completion of the PRO instrument by patients remains uncertain. Third, the reasons for missing HRQoL questionnaires should be documented to identify the mechanism and pattern of missing data. In summary, it is crucial to reduce the magnitude of missing data and develop strategies for handling missing data while designing PRO studies in recipients of CAR-T cell therapy, especially given the high anticipated incidence of acute toxicities. Furthermore, to avoid survey fatigue especially in the acute phase, designing optimal instruments that are reliable and pose minimal burden to patients is important.

How to Handle Response Shift?

Response shift, a well-recognized phenomenon in QoL research, is defined as a change in individual's value, internal standards, and conceptualization of HRQoL, which can make longitudinal comparison challenging [68,69]. In long-term survivors of HSCT this phenomenon is well documented, with patients reporting improved psychological and interpersonal growth after transplant despite having a profound negative impact on physical functioning [70,71]. Although the long-term trajectory of patients receiving CAR-T cell therapy is not known at present, there is a potential for long-lasting remission and possibly cure in a subset of patients. Two commonly used methods for longitudinal analysis of HRQoL are linear mixed model for repeated measures and time-to-event analysis. One way to address response shift is by considering the best previous score instead of the baseline score as the reference value in time-to-event analysis [68,69]. The International Society of Quality of Life has created a special interest group to understand when and why response shift occurs, which will enable investigators to recognize and account for response shift in appropriate circumstances and develop methodologic solutions for dealing with response shift. Investigators and clinicians need to be cognizant of this phenomenon while interpreting long-term HRQoL data after CAR-T cell therapy.

GENERAL BARRIERS TO IMPLEMENTATION

The barriers to implementation of PRO have been broadly divided into 2 categories: logistical and technologic issues [47]. Despite robust evidence of the utility of PROs, integrating PRO assessment with routine oncology care remains challenging. It requires engagement of physicians and ancillary staff along with a smooth operational workflow. Several institutions and healthcare systems have successfully integrated electronic PRO assessment into their workflow, which can inform us regarding the challenges and strategies for successful implementation [48]. One of the critical components for successful integration of PRO is designing a mechanism to address the issues raised by patients without overwhelming the administrative burden for caregivers. In the organization-wide PRO initiative at Dartmouth-Hitchcock [48], 1 of the key implementation steps is to categorically define roles in the clinic regarding who will be looking at the PRO data and how will that data be used. Clinical trials measuring PROs with CAR-T cell therapy should explicitly mention in the protocol whether collection of data will be solely for research purposes or inform real-time patient care. One of the potential challenges could be that patients may travel to referral centers for CAR-T cell therapy and then transition back to local centers. In that setting details on who will collect and follow the long-term PRO data should be decided a priori. Our general recommendations on incorporation of PRO in CAR-T cell therapy, both in the setting of clinical trials and routine practice, are summarized as follows:

- We recommend measuring PROs at baseline before lymphodepleting chemotherapy, at least weekly in the acute phase after CAR-T cell infusion, monthly until 1 year, and yearly thereafter.
- Core PRO domains to consider are physical functioning, disease symptoms, and symptomatic AEs. Because neurotoxicity is a unique adverse effect of CAR-T cell therapy, measurement of cognitive functioning can be considered.
- PROMIS questionnaires should be considered for measurement of PROs in CAR-T recipients, which will help in standardization and enable comparative effectiveness studies. Measurement of symptomatic AEs with PRO-CTCAE can provide valuable information on tolerability.
- Missing PRO data should be minimized, and reasons for missing data should be clearly documented. In the acute phase, when severe toxicity in expected, auxiliary data like CARTOX-10 assessment and CRS grading will be helpful in statistical analysis.
- Qualitative studies like structured interviews and focus groups should be performed to obtain direct patient input on PRO domains and instruments.

CONCLUSION

With overwhelming evidence regarding the value of PRO assessment in cancer, it is our responsibility to measure patients' perspective of the impact of new treatments on their

overall health and well-being. Multi-institutional collaboration and creation of a centralized database is needed to characterize core PRO domains including physical function, symptomatic AEs, and disease-related symptoms in patients receiving CAR-T cell therapies. Rigorously developed universal PRO tools like PROMIS and PRO-CTCAE are already available that can be used in CAR-T clinical trials. As multiple targets for CAR-T cells are being recognized in various malignancies, future comparative effectiveness studies evaluating different CAR constructs, cell dose, target antigen, and conditioning chemotherapy can use PROs as an endpoint for evaluation of toxicity and HRQoL. Qualitative studies like focus groups and structured interviews should be conducted to obtain direct patient input regarding PRO instruments and domains, which will ensure we are measuring what really matters to our patients.

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