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Chimeric Antigen Receptor T-cell Therapy in Hematologic Malignancies and Patient-reported Outcomes: A Scoping Review

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ABSTRACT

The inclusion of patient-reported outcome (PRO) measures in chimeric antigen receptor (CAR) T-cell therapy research is critical for understanding the impact of this novel approach from a unique patient standpoint. We performed a scoping review to map the available literature on the use of PRO measures in CAR T-cell therapy studies of patients with hematologic malignancies published between January 2015 and July 2022. Fourteen studies were identified, of which 7 (50%) were investigational early-phase trials, 6 (42.9%) were observational studies, and 1 (7.1%) was a pilot study. The EQ-5D and the PROMIS-29 were the 2 most frequently used PRO measures, being included in 6 (42.9%) and 5 (35.7%) studies, respectively. Despite differences in study designs, there seems to be evidence of improvements over time since CAR T-cell infusion in important domains such as physical functioning and fatigue, at least in patients who respond to therapy. Overall, the studies identified in our review have shown the added value of PRO assessment in CAR T-cell therapy research by providing novel information that complements the knowledge on safety and efficacy. However, there are several questions which remain to be answered in future research. For example, limited evidence exists regarding patient experience during important phases of the disease trajectory as only 4 (28.6%) and 5 (35.7%) studies provided information on PROs during the first 2 weeks from CAR T-cell infusion and after the first year, respectively. Time is ripe for a more systematic implementation of high-quality PRO assessment in future clinical trials and in real-life settings of patients treated with CAR T-cell therapy.

INTRODUCTION

Chimeric antigen receptor (CAR) T-cell therapy is an innovative therapy that has the potential to change the clinical outcomes of many patients with hematological malignancies. Adoptive T-cell therapies, which have been genetically engineered for a new antigen-specificity[1], showed impressive response rates and response durability even in patients with advanced relapsed/refractory (R/R) hematologic malignancies such as acute B-lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL).[2–15] More recently, treatment with B-cell maturation antigen (BCMA)–directed CAR T cells also resulted in frequent and deep responses in heavily pretreated patients with R/R multiple myeloma (MM).[16,17]

The first 2 CAR T-cell therapies approved in the United States and Europe for relapsed/refractory B aggressive NHLs in the third line and beyond were axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel). These approvals were based on the results of the ZUMA-1 and JULIET studies, respectively, demonstrating a 30% to 50% complete response (CR) rate and a 30% to 40% long-term disease-free survival after a single infusion.[3,4,9,10] To date, the following 6 CAR T-cell therapies have been approved: tisa-cel, axi-cel, lisocabtagene maraleucel (liso-cel), brexucabtagene autoleucel (brexu-cel), idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) for the treatment of R/R ALL, R/R NHL and R/R MM, respectively.[18,19]

However, during clinical testing, all CAR T-cell therapies demonstrated severe and different toxicities compared to those observed in other cellular therapies (such as autologous or allogeneic hematopoietic stem cell transplantation (SCT) or donor lymphocyte infusion) or traditional chemotherapies, suggesting profound, and generalized immune system activation.[20–22] The 2 most commonly observed toxicities are cytokine-release syndrome (CRS), characterized by high fever, hypotension, hypoxia, and/or multiorgan toxicity; and immune effector cell-associated neurotoxicity syndrome (ICANS), typically characterized by delirium, encephalopathy, aphasia, lethargy, difficult concentrating, agitation, tremor, confusion, and

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occasional seizures and cerebral edema.[23,24] While CRS toxicity typically occurs within the first 2 weeks after CAR T-cell therapy,[23] the manifestation of ICANS can occur concurrently with high fever and other CRS symptoms,[25–28] or shortly after CRS subsides, or as a delayed form in the third or fourth week after CAR T-cell therapy.[21,23,27] Furthermore, the observation that 3%–10% of neurologic events in the majority of early trials remain unresolved at the time of study reporting (median follow-up of 3 to 28 months or even less, up to about 12 months in the case of myeloma)[2,9,16,29,30] and anecdotal reports of long-term sequelae of neurotoxicity,[31] mild memory impairment,[32] or confusion, and disorientation followed by expressive aphasia,[33] point to the importance of monitoring for the occurrence of late neurologic events.[34] There is also evidence indicating that patients who receive CAR T-cell therapy may experience long-term adverse events (AEs) such as prolonged B-cell aplasia, hypogammaglobinemia, prolonged cytopenia, infections, and autoimmune reactions.[2,10,34,35]

While evidence of the clinical efficacy and safety of CAR T-cell therapy continues to accumulate, it is also important to better understand the impact of this therapy from the unique patient's standpoint. Inclusion of patient-reported outcome (PRO) measures in cancer clinical trials, for example, may be critical to more thoroughly evaluate benefit/risk profile of a treatment by complementing physicians' understanding of toxicity and informing tolerability.[36,37] Some examples of the added value of PROs in clinical research in hematology are available.[38]

A recent review of the available PRO evidence for patients with hematologic malignancies receiving CAR T-cell therapy was published by Kamal et al,[39] and only 3 published studies were identified up to April 2020. Given the increasing interest in this area of research, we performed a scoping review to map available literature on the use of PRO measures in CAR T-cell therapy studies, to summarize the main findings and gain insights for future research directions.

METHODS

Identification of relevant studies

We performed a scoping review[40] based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR).[41] No protocol was published for this review. We conducted a systematic literature search in PubMed, Cochrane and Web of Science databases to identify CAR T-cell therapy studies in patients with hematologic malignancies which have assessed PROs and were published from January 2015 to July 2022. The starting point of the time window was selected considering that the first CAR T-cell therapy was only approved by the US FDA in 2017.[42] The following searching strategy was used: "quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR sexual OR functioning) and ("chimeric antigen receptor" OR " CAR") AND (gammopathy OR myelodysplastic OR myelodysplasia OR leukemia OR leukaemia OR lymphoma OR myeloma OR myelofibrosis OR myeloproliferative OR polycythemia OR polycythaemia OR thrombocythemia OR thrombocythaemia). Additional publications were identified by hand searching the reference lists of these articles or consulting relevant study publication lists at http://clinicaltrials.gov.

An independent search was also performed on PubMed using the DistillerSR software[43] for abstract and full-text screening (see the search terms used in Suppl. Appendix 1). Only English language articles were considered, and no restrictions were included in the search field description. Case reports, reviews, and articles on laboratory or in vitro researches were excluded by title and abstract screening. If a selected study had multiple publications, information from all related papers was extracted to maximize the quality of the information in our review.

Selection criteria

Types of participants

Participants were patients diagnosed with any hematologic malignancy, regardless of the stage of the disease and patients' age. Studies including mixed hematologic malignancies were still considered as long as did not include patients with solid tumors.

Types of intervention

Interventions included any kind of CAR T-cell therapy either used alone or in combination with other drugs. Any CAR T-cell product was considered, regardless of its approval from regulatory agencies.

Types of outcome measures examined

Studies incorporating PRO measures were considered. Publications of study protocols were excluded as they do not report original PRO results. Studies reporting cost-utility analyses only were excluded as beyond the scope of this review.

Types of studies

All types of studies were considered regardless of their research design, providing they reported quantitative analyses. Conference abstracts, studies reporting results from qualitative analyses or reporting results from online surveys were excluded. No restriction in the number of patients enrolled was applied.

Data extraction and evaluation

A predefined data extraction form was used to collect the following information from each eligible study for this review: (1) basic study characteristics (ie, study acronyms if available, multicenter study [y/n], study design); (2) clinical details (ie, type of hematologic disease, type of CAR T-cell product, patient's age, number of patients); (3) PRO assessment characteristics (ie, PRO measure/s used, type of PRO analysis [longitudinal/cross-sectional] and PRO assessment schedule). For descriptive purposes, this latter aspect was classified as occurring during the following: acute phase, subacute phase and long-term follow-up.[44] More specifically, we also assessed whether a PRO assessment occurred within the first 2 weeks after the procedure, as CRS toxicity typically occurs in this period[23]; (4) summary of PRO findings. With regard to the latter aspect, information on the statistical significance of PRO results (ie, based on *P* values or confidence intervals) was also extracted if available in the manuscript. Improvements and/or deterioration of PROs from baseline assessment were reported for each timepoint, in the case of a longitudinal PRO analysis. When no information on statistical significance was provided in the article or none of the PROs significantly differed from the baseline assessment, we summarized descriptive PRO findings based on what the authors reported in the article. Data extraction was performed independently by 2 reviewers (LC, FS, or JMR). If discrepancies in the evaluation of any item occurred, the reviewers revisited the papers to reconcile any differences. A third senior reviewer (FE) was consulted if no consensus was achieved.

RESULTS

The literature search identified 2473 records published from January 1, 2015, until July 1, 2022, that were screened for eligibility. Of these, we retrieved a total of 14 eligible studies reporting PRO results.[14,15,45–56] Details of the search strategy and selection process of the articles included in this review were documented according to the PRISMA guidelines[57] and are reported in Figure 1.

Overview of study characteristics

All eligible studies enrolled patients with advanced hematologic diseases: twelve studies examined patients with B-cell lymphoproliferative malignancies treated with CD19-directed CAR T cells, one study examined patients with multiple myeloma treated with BCMA-directed CAR T cells and one study examined patients with either B-cell lymphoproliferative malignancy or multiple myeloma treated with any type of CAR T-cell therapy.

Overall, 1162 (range 12–269) patients treated with CAR T-cell therapy were included in the selected studies. Most of the studies (n = 9, 64.3%) enrolled fewer than 100 patients. In 7 studies (50%) the median or mean age of treated patients was 60 years or older. Seven studies (50%) were investigational early-phase trials (5 phase 2 trials, one phase 1 trial, 1 seamless design trial), one (7.1%) was a pilot study and 6 (42.9%) were observational studies.

Twelve studies (85.7%) examined longitudinal PRO assessments including PRO collection at baseline (prior and/or on the same day of CAR T-cell infusion); 2 studies (14.3%) had a cross-sectional design for PRO evaluation.

In most studies (n = 11, 78.6%), PROs were assessed with more than 1 measure. The EQ-5D was the most frequently used one (n = 6, 42.9%), followed by the Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) being used in 5 studies (35.7%) (Table 1).

Overview of PRO findings from early-phase clinical trials

Of the 7 clinical trials describing PROs in hematologic patients treated with CAR T-cell therapy, none were randomized clinical trials (RCT) and all trials had a longitudinal design of PRO evaluation (Table 2).

The ELIANA[45] and JULIET[47] studies assessed the health-related quality of life (HRQoL) impact of tisa-cel, administered to pediatric and young adult patients with R/R B-ALL and adult patients with R/R diffuse large B-cell lymphoma (DLBCL), respectively. Laetsch et al described a rapid and sustained improvement in broad aspects of HRQoL, measured with PedsQL and EQ-5D VAS, in pediatric and young adult R/R B-ALL patients who were in second or greater bone marrow relapse, chemorefractory, relapsed after allogeneic stem cell transplant, or were otherwise ineligible for allogeneic stem cell transplant.[45] PRO improvements from baseline were observed from day 28 after infusion as measured with PedsQL total score and EQ-5D VAS, albeit lower mean score changes were reported in patients who had severe CRS or neurotoxicity. Clinically meaningful improvements from baseline in all HRQoL subscales/dimensions (eg, physical functioning, emotional functioning, school functioning and social functioning) were achieved by month 3 and were confirmed at later timepoints (months 6, 9, and 12), irrespective of severe toxicity occurrence. Maziarz et al reported that adult patients with R/R DLBCL, who responded to tisa-cel and have had at least 2 or more lines of prior therapy including rituximab and anthracycline, and either had relapsed after, were ineligible for, or did not consent to autologous hematopoietic stem cell transplant, had clinically meaningful and long-term improvement in HRQoL, measured with FACT-Lym and SF-36.[47] The lack of PRO assessments in patients who did not respond to tisa-cel therapy (as they discontinued the study due to death, disease progression or loss to follow-up) and the low completion rates of PRO assessments at months 12 and 18,

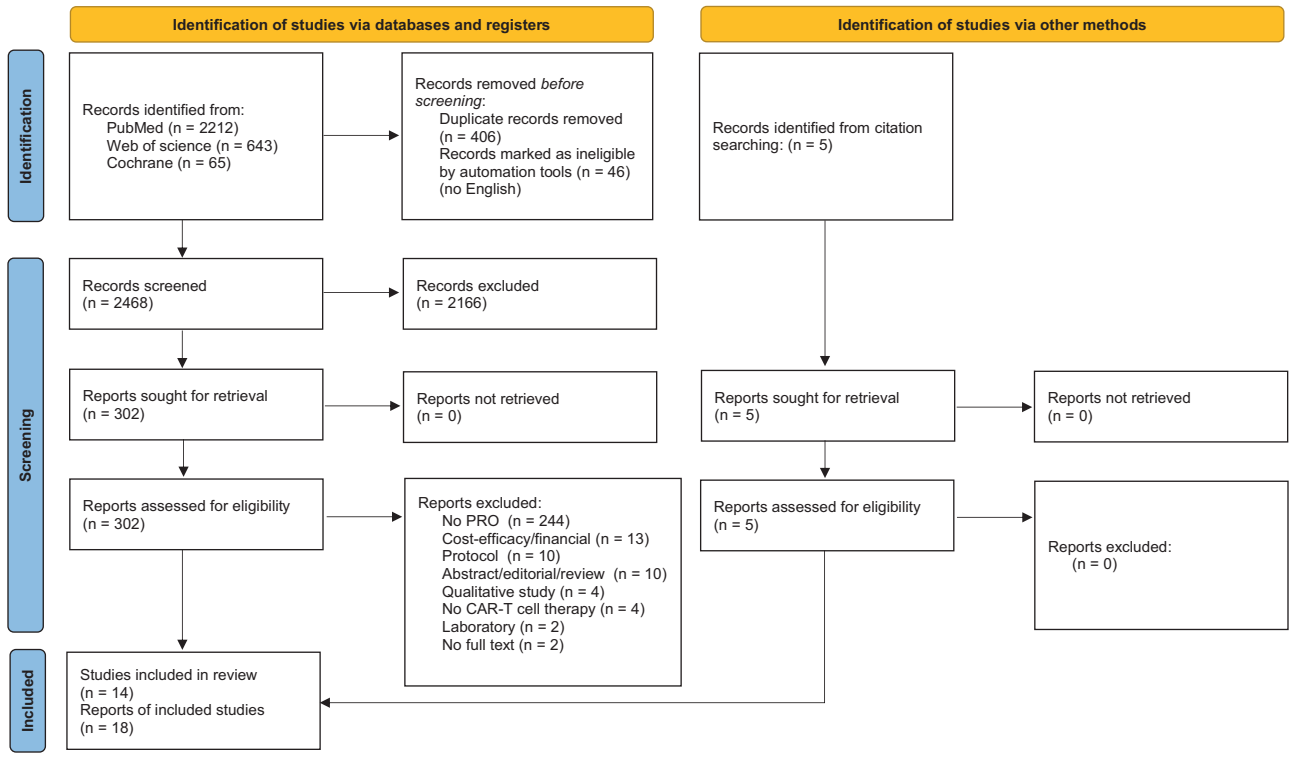

Figure 1. PRISMA 2020 flow diagram of articles selection process. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Table 1

Study Characteristics (N = 14)

Variables	No. (%)
Type of disease	
Large B-cell lymphoma (±other hematologic malignancies)	8 (57.2)
B-cell acute lymphoblastic leukemia	2 (14.3)
Diffuse large B-cell lymphoma	2 (14.3)
Multiple myeloma	1 (7.1)
Mantle cell lymphoma	1 (7.1)
CAR-T product[a]	
Tisagenlecleucel	6 (42.9)
Axicabtagene ciloleucel	5 (35.7)
Brexucabtagene autoleucel	3 (21.4)
Lisocabtagene maraleucel	1 (7.1)
Idecabtagene vicleucel	1 (7.1)
Bispecific LV20.19 CAR T cells	1 (7.1)
Anti-CD19 CAR T Lymphocytes	1 (7.1)
Unknown	1 (7.1)
Multicenter study	
Yes	7 (50)
No	7 (50)
Type of PRO analysis	
Longitudinal	12 (85.7)
Cross-sectional	2 (14.3)
Most frequently PRO measures[b,c]	
EQ-5D questionnaire	6 (42.9)
PROMIS questionnaires	5 (35.7)
EORTC questionnaires	3 (21.4)
FACIT questionnaires	2 (14.3)
PRO-CTCAE	2 (14.3)

[a]Some studies used more than one CAR-T product.

[b]More than one PRO measure could be used.

[c]If one study used more than one questionnaire from the same family (eg, EORTC QLQ-C30 and EORTC QLQ-MY20), it counted as one.

CAR T = chimeric antigen receptor T-cell; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System.

impaired the ability of this study to explore the relationship between treatment effect and HRQoL[47].

The ZUMA-2[14] and ZUMA-3[15] studies reported the HRQoL impact of brexu-cel in adult patients with R/R mantle cell lymphoma (MCL) and R/R ALL, respectively. Wang et al[14] observed that adult R/R MCL patients, who had received up to 5 previous therapies including anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib, reported a transient decline in HRQoL at week 4 after brexu-cel infusion, followed by return or improvement of HRQoL status at 3 and 6 months, as measured with descriptive statistics of EQ-5D scores (both the VAS score and the dimension of mobility, self-care, and usual activity). Shah et al[15] indicated that the majority of evaluable adult patients with R/R ALL (ie, with first CR of 12 months or less, or after at least 2 previous lines of systemic disease or after allogeneic hematopoietic stem cell transplant and with an ECOG of 0-1) experienced improved or stable HRQoL over time after brexu-cel infusion, as measured with EQ-5D-5L (both the VAS score and EQ-5D dimensions). In this brief descriptive analysis, the proportion of patients reporting no problem in 3 dimensions of EQ-5D (ie, mobility, usual activity and self-care) decreased at one month after infusion, but starting from month 3, this proportion of patients reporting no problem reached stably higher levels than those at baseline across all 5 EQ-5D dimensions.[15]

In the TRANSCEND NHL001 study,[49] R/R LBCL adult patients, who had previously received 2 or more previous lines of systemic treatment including chemoimmunotherapy containing anti-CD20 and anthracycline, reported a significant initial deterioration of physical functioning at 1 month after liso-cel treatment followed by significant improvement at 2, 9, and 12 months.[49] Patrick et al described clinically meaningful improvements in global health status/QoL and fatigue, as measured with the EORTC QLQ-C30, as early as 2 months after liso-cel infusion and maintained thereafter through 18 months.[49] The EORTC QLQ-C30 pain score profile over time after liso-cel infusion showed significant improvement at 2 months, deterioration to near-baseline value at 3 to 9 months, and then improvements at 12 months.[49] The mean EQ-5D-5L index score was significantly increased at 2, 12, and 18 months.[49] Despite a small number of treatment nonresponders completed PRO assessments at later timepoints, PRO improvements at any timepoint after liso-cel infusion were described as more frequent in treatment responders than in treatment nonresponders.[49] The median time to first clinically meaningful improvement was shorter in treatment responders than in nonresponders in global health status/QoL, fatigue, and pain. Individual-level PRO analysis revealed that more patients reported clinically meaningful improvements in HRQoL and symptom burden than clinically meaningful deterioration at each timepoint.[49]

In the KarMMa study,[52] triple-class exposed R/R MM patients who received ide-cel infusion as the fourth line or later treatment reported statistically and clinically meaningful improvements in most PROs, including pain and disease symptoms by month 1, and, later on, including fatigue, pain, physical functioning, cognitive functioning, global health status/QoL, disease symptoms, and side effects from month 2 through month 9, as measured with the EORTC QLQ-C30 and QLQ-MY20. Improvements in fatigue and physical functioning generally persisted through 18 months. Patients' baseline HRQoL scores (fatigue, pain, global health status/QoL, physical and cognitive functioning) were worse than those of the re-weighted general population at baseline and became comparable to those of the general population at 1 to 3 months and throughout month 18.[52]

Recently, the trajectory of self-reported depression, sleep quality, fatigue, anxiety, and pain in 15 R/R NHL or CLL patients, who received bispecific anti-CD19 anti-CD20 CAR T cells (LV20.19) in a phase 1 trial and survived at day 28 after infusion, revealed a significant reduction only in depression between day 14 and day 90 after CAR T-cell infusion and, a correlation between changes in depression scores and in blood kynurenine concentration, as a possible biomarker of depression, during study timepoints.[54]

Overview of PRO findings in pilot or observational studies

Among the 6 eligible observational studies and one pilot study, 2 had a cross-sectional design for PRO assessment, and 5 analyzed PRO changes over time (Table 3). These studies mainly described symptom experience of patients over time after CAR T-cell infusion and contributed to defining the unique toxicity profile of CAR T-cell therapy.

Ruark et al[46] observed that, at the median follow-up of 3 years after CAR T-cell infusion, 40 long-term hematologic cancer survivors enrolled at Fred Hutchinson Cancer Center (Seattle, USA) reported an overall good self-neuropsychiatric status (ie, PROMIS-Global Health and PROMIS-29) that was similar to that of the general US population.[46] However, nearly 50% of patients reported at least one cognitive difficulty and/or clinically meaningful depression and/or anxiety. Younger age, longer time since treatment, depression pre-CAR T-cell, and acute neurotoxicity were suggested as potential risk factors for adverse neuropsychiatric outcomes after CAR T-cell infusion to be validated for planning of interventional strategies.[46]

The longitudinal assessment of HRQoL and symptom burden in 103 adult NHL patients over a period of 3 months after axi-cel infusion[48] at the Moffitt Cancer Center (Tampa, USA) suggested that improvement in physical functioning, reduction

Table 2

Overview of PRO Findings in Early-phase Clinical Trials on CAR T-cell Therapy in Patients With Hematologic Malignancies

Reference	Study Acronym	Disease	CAR-T Product	Number of Patients[a]	Age of Patients (Y)[b]	PRO Measures[c]	PRO Analysis (Cross-sectional/ Longitudinal)	PRO Evaluation Within 2 Wks From Infusion	Phases of CAR T-cell Therapy PRO Assessment[d]	PRO Findings[e]
Laetsch et al[45] Maude et al[2]	ELIANA	B-ALL	tisa-cel	75	11 (range 3–23)	PedsQL; EQ-5D	Longitudinal	No	Acute; subacute	**Statistically significant changes from baseline:** *Day 28* Improvement: PedsQL (total score and emotional functioning); EQ-5D VAS. *Month 3, Month 6, Month 9, Month 12* Improvement: PedsQL (total score, emotional functioning, social functioning, school functioning, physical functioning, and psychosocial health summary score); EQ-5D VAS.
Maziarz et al[47]	JULIET	DLBCL	tisa-cel	115	56 (range 22–76)	FACT-Lym; SF-36	Longitudinal	No	Acute; subacute; long-term follow-up	**Based on descriptive findings:** Among patients who responded to therapy, clinically meaningful improvements from baseline were observed in all timepoints (3, 6, 12 and 18 mo) for all FACT scores (FACT-G TS, FACT-Lym S, FACT-Lym TOI, and FACT-Lym TS) and for 5 of 8 SF-36 subscales (general health, vitality, physical functioning, role-physical, and social functioning).
Wang et al[14]	ZUMA-2	MCL	brexu-cel	68	65 (range 38–79)	EQ-5D	Longitudinal	No	Acute; subacute	**Based on descriptive findings:** EQ-5D scores for all scales revealed decreases from baseline in HRQoL at week 4; better scores in mobility, self-care, usual activities, and overall health were observed by month 3, with overall health (as measured with EQ-5D VAS) returning to baseline status or better in most patients by month 6.
Patrick et al[49] Abramson et al[13]	TRANSCEND NHL 001	LBCL	liso-cel	269	63 (IQR 54–70)	EORTC QLQ-C30; EQ-5D-5L	Longitudinal	No	Acute; subacute; long-term follow up	**Statistically significant changes from baseline in primary scales:** *Month 1* Improvement: EORTC QLQ-C30 (global health status/QoL, pain). Deterioration: EORTC QLQ-C30 (physical functioning). *Month 2* Improvement: EORTC QLQ-C30 (global health status/QoL, pain, fatigue, physical functioning); EQ-5D-5L index score. *Month 3, Month 6* Improvement: EORTC QLQ-C30 (global health status/QoL, fatigue). *Month 9* Improvement: EORTC QLQ-C30 (global health status/QoL, fatigue, physical functioning). *Month 12* Improvement: EORTC QLQ-C30 (global health status/QoL, pain, fatigue, physical functioning); EQ-5D-5L index score. *Month 18* Improvement: EORTC QLQ-C30 (global health status/QoL, fatigue); EQ-5D-5L index score.

(Continued)

Table 2 (Continued)

Reference	Study Acronym	Disease	CAR-T Product	Number of Patients[a]	Age of Patients (Y)[b]	PRO Measures[c]	PRO Analysis (Cross-sectional/ Longitudinal)	PRO Evaluation Within 2 Wks From Infusion	Phases of CAR T-cell Therapy PRO Assessment[d]	PRO Findings[e]
Shah et al[15]	ZUMA-3	B-ALL	brexu-cel	55	40 (IQR 28–52)	EQ-5D-5L	Longitudinal	No	Acute; subacute	**Based on descriptive findings:** The proportion of patients reporting no problems in mobility, usual activities, and self-care decreased at day 28 after CAR T-cell infusion. Starting at month 3, the proportion of patients reporting no problems rebounded (mobility and pain/discomfort) or reached higher levels (self-care, usual activities, and anxiety/depression). By month 12, the proportions of patients reporting no problems were higher than those at screening across all 5 dimensions. The median VAS score increased from 70.0 at screening to 87.5 by month 12. Most patients maintained stable VAS scores or improved over time.
Delforge et al[52] Munshi et al[16]	KarMMa	MM	ide-cel	128	61 (33–78)	EORTC QLQ-C30, EORTC QLQ-MY20; EQ-5D-5L	Longitudinal	No	Acute; subacute; long-term follow up	**Statistically significant changes from baseline in primary scales:** *Day 1* Deterioration: EORTC QLQ-C30 (fatigue, global health status/QoL); EORTC QLQ-MY20 (side effects of treatment). *Month 1* Improvement: EORTC QLQ-C30 (pain); EORTC QLQ-MY20 (disease symptoms). *Month 2, Month 3, Month 4, Month 5, Month 6, Month 9* Improvement: EORTC QLQ-C30 (fatigue, pain, physical functioning, cognitive functioning, global health status/QoL); EORTC QLQ-MY20 (disease symptoms, side effects of treatment). *Month 12* Improvement: EORTC QLQ-C30 (fatigue, pain, physical functioning, global health status/QoL); EORTC QLQ-MY20 (disease symptoms, side effects of treatment). *Month 15* Improvement: EORTC QLQ-C30 (fatigue, pain); EORTC QLQ-MY20 (disease symptoms, side effects of treatment). *Month 18* Improvement: EORTC QLQ-C30 (fatigue, physical functioning).
Knight et al[54] Shah et al[58]	NA	NHL, CLL	Bispecific LV20.19 CAR T cells	22	57 (range 38–72)	IDAS ; FSI; PSQI; BPI	Longitudinal	Day +14 postinfusion	Acute; subacute	**Statistically significant changes from baseline:** *Day 90* Improvement: Depression (IDAS)

[a]The number of patients treated with CAR-T, regardless of whether they have or not a baseline PRO assessment completed.

[b]In this column, we reported the median age and/or age range or standard deviation or interquartile range of the overall sample. If median age was unavailable, we detailed the mean age as reported by the authors.

[c]We listed only PRO instruments/scales described in the articles, as reported by the authors. The PRO instrument described in the protocol but not in the article are excluded.

[d]According to the classification proposed by Lasiter et al.[44]

[e]In this column, we reported, for each timepoint, the PRO scales which significantly improved or deteriorated from baseline. When no information on statistical significance (ie, *P* value, confidence intervals) was reported or none of the PRO scales significantly differ from baseline, we summarized information on PRO findings, based on what the authors reported in the abstract, results or discussion of the article, regardless of their statistical or clinical significance.

B-ALL = B-cell acute lymphoblastic leukemia; BPI = Brief Pain Inventory; brexu-cel = brexucabtagene autoleucel; CAR T = chimeric antigen receptor T-cell; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; EORTC = European Organization for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; FACT-Lym = Function Assessment of Cancer Therapy-Lymphoma; FSI = Fatigue Symptom Inventory; HRQoL = health-related quality of life; IDAS = Inventory of Depression and Anxiety Symptoms; ide-cel = idecabtagene vicleucel; IQR = interquartile range; LBCL = Large B-cell lymphoma; liso-cel = lisocabtagene maraleucel; MCL = mantle cell lymphoma; MM = multiple myeloma; NA = not available; NHL = non-Hodgkin Lymphoma; PedsQL = Pediatric Quality of Life Inventory; PRO = patient-reported outcome; PSQI = Pittsburgh Sleep Quality Index; QLQ = quality of life questionnaire; QoL = quality of life; SF-36 = Medical Outcome Study 36-Item Short Form Health Survey; tisa-cel = tisagenlecleucel; VAS = visual analog scale.

Table 3

Overview of PRO Findings in Pilot or Observational Studies on CAR T-cell Therapy in Patients With Hematologic Malignancies

Reference	Study Acronym	Disease	CAR-T Product	Number of Patients[a]	Age of Patients (Y)[b]	PRO Measures[c]	PRO Analysis (Cross-sectional/ Longitudinal)	PRO Evaluation Within 2 Wks From Infusion	Phases of CAR T-cell Therapy PRO Assessment[d]	PRO Findings[e]
Ruark et al[46]	NA	ALL; CLL, NHL	Anti-CD19 CAR-T Lympho-cytes[f]	40	57 (range 26–76)	PROMIS Global Health; PROMIS–29; ad-hoc questionnaire	Cross-sectional	No	Long-term follow-up	**Based on descriptive findings:** Mean self-reported PROMIS domains of global mental health, global physical health, social function, anxiety, depression, fatigue, pain, and sleep disturbance of long-term survivors after CAR T-cell therapy was not clinically meaningfully different from the general US population. However, nearly 50% of patients reported at least one cognitive difficulty and/or clinically meaningful depression and/or anxiety. Younger age, longer time since treatment, depression pre-CAR T-cell and acute neurotoxicity may be risk factors for long-term neuropsychiatric problems. Having more cognitive difficulties was associated with worse global mental and physical health as well as more pain, fatigue, sleep disturbance, depression and anxiety.
Hoogland et al[48]	NA	NHL	axi-cel	103	Mean 60.6 (SD 12.3)	PROMIS–29, PRO-CTCAE	Longitudinal	Day +14 from infusion (PRO-CTCAE)	Acute; subacute	**Statistically significant changes from baseline:** *Day 90* Improvement: PROMIS–29 (fatigue, pain, physical functioning). Deterioration: PROMIS-29 (anxiety) *Changes over time in toxicity*[g] PRO-CTCAE (dry mouth, decreased appetite, nausea, cough, hair loss, hand-foot syndrome, problems with concentration, problems with memory, headache, fatigue, aching muscles).
Maillet et al[50]	NA	NHL	axi-cel; tisa-cel	56	Mean 58 (SD 14)[h]	HADS, QMRP	Longitudinal	No	Subacute	**Statistically significant changes from baseline:** *Months 6–12* Improvement: QMRP (prospective memory)
Wang et al[51]	NA	AL, LBCL	axi-cel; tisa-cel	60	58.9 (range 18.7–78.6)	MDASI, PROMIS–29, EQ-5D-5L, 22 items from MDASI library, single-item HRQoL	Cross-sectional	Yes[i]	Acute; subacute	**Based on descriptive findings:** The first 90 d after CAR T-cell infusion represented the most symptomatic period, in which >10% of patients rated 18 symptoms from the MDASI as severe. Physical functioning was significantly worse in patients who completed PRO assessment during the first 30 d compared with those who completed PRO assessment after 90 d and up to 1 y after CAR T-cell infusion. Compared with patients who had mild CRS or neurotoxicity (grades 0–1), patients who developed grades 2–4 toxicities persistently reported multiple severe symptoms after 30 d following therapy.
Ram et al[53]	NA	DLBCL	axi-cel; tisa-cel	41	Mean 76.2 (SD 4.4)	EORTC QLQ-C30	Longitudinal	No	Acute; subacute	**Statistically significant changes from baseline:** *Month 3* Improvement: EORTC QLQ-C30 item overall health perception
Oswald et al[55]	NA	MM, MCL, DLBCL, CLL	Unknown	12	Mean 66 (53–77)	CCI; FACT-G; PROMIS–29; FACT-G7; PRO-CTCAE, ad-hoc surveys	Longitudinal	Days 1–6 (FACT-G7), day 7 and day 14 (FACT-G, PROMIS-29 and PRO-CTCAE) from infusion	Acute; subacute	**Based on descriptive findings:** The average FACT-G total HRQoL scores were within the normal range at all timepoints. However, average physical well-being was clinically low on day 7, and average functional well-being was clinically low on days 7–30. On the PROMIS scales, average fatigue was mild on days 0–30. Average pain interference was mild on day 14. Average physical function was mildly impaired at baseline and day 0, moderately impaired on days 7–30, and returned to mildly impaired on day 60. Average ability to participate in social roles and activities was mildly impaired on days 7–30. All other PROMIS scale scores were in the normal range. In the week following CAR T-cell infusion, average FACT-G7 total scores indicated low HRQoL on days 2 and 4. Preliminary data patterns suggested that participants with better treatment response (vs progressive disease) had a higher toxicity burden (as measured with the PRO-CTCAE).

(Continued)

Table 3 (Continued)

Reference	Study Acronym	Disease	CAR-T Product	Number of Patients[a]	Age of Patients (Y)[b]	PRO Measures[c]	PRO Analysis (Cross-sectional/ Longitudinal)	PRO Evaluation Within 2 Wks From Infusion	Phases of CAR T-cell Therapy PRO Assessment[d]	PRO Findings[e]
Barata et al[56]	NA	LBCL, FL, MCL	axi-cel; tisa-cel; brexu-cel	118	Mean 61 (SD 12)	ECog; PROMIS–29	Longitudinal	No	Subacute; long-term	**Based on descriptive findings:** Mean levels of perceived cognition did not change from baseline to day 90 but worsened from day 90 to day 360 in global cognition and in the domains of memory, language, organization, and divided attention. Greater baseline fatigue, anxiety, and depression were associated with worse global cognition at day 90. Patients with more severe ICANS post-CAR-T reported worse global cognition at day 360.

[a]The number of patients with hematologic malignancies treated with CAR-T, regardless of whether they have or not a baseline PRO assessment completed.
[b]In this column, we reported the median age and/or age range or standard deviation or interquartile range of the overall sample. If median age was unavailable, we detailed the mean age as reported by the authors.
[c]We listed only PRO instruments/scales described in the articles, as reported by the authors. The PRO instrument described in the protocol but not in the paper are excluded.
[d]For descriptive purposes, we use the classification proposed by Lasiter et al.[44]
[e]In this column, we reported, for each timepoint, the PRO scales which significantly improved or deteriorated from baseline. When no information on statistical significance (ie, *P* value, confidence intervals) was reported or none of the PRO scales significantly differ from baseline, we summarized information on PRO findings, based on what the authors reported in the abstract, results or discussion of the article, regardless of their statistical or clinical significance.
[f]Autologous Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing T Lymphocytes (clinical trial NCT01865617).
[g]Mixed models with linear and quadratic effects of time were used to evaluate change in toxicities controlling for baseline.
[h]Age refers to patients eligible for mid-term evaluation (n = 27). Age for the overall sample was not available.
[i]Patients were approached at any time within the first 12 months after CAR T-cell therapy and, after providing consent, completed the PRO questionnaires. Of these, only a subgroup of patients completed the PRO questionnaires within 2 weeks from infusion.
[j]Authors did not report the items/scales according to the official scoring system of the EORTC QLQ-C30. For example, QLQ-C30 items 29 (overall health) and 30 (overall QoL) are reported separately instead of as unique scale (ie, Global health status/QoL).

AL = acute leukemia; ALL = acute lymphoblastic leukemia; axi-cel = axicabtagene ciloleucel; brexu-cel = brexucabtagene autoleucel; CAR T = chimeric antigen receptor T-cell; CCI = Charlson Comorbidity Index; CLL = chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; CRS = cytokine-release syndrome; DLBCL diffuse large B-cell lymphoma; ECog = Everyday Cognition Questionnaire; EORTC = European Organization for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; FL = follicular lymphoma; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health-related Quality of Life; ICANS = immune effector cell-associated neurotoxicity syndrome; LBCL = Large B-cell lymphoma; MCL = mantle cell lymphoma; MDASI = MD Anderson Symptom Inventory; MM = multiple myeloma; NHL = non-Hodgkin Lymphoma; NA = not available; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; QLQ = quality of life questionnaire; QMRP = Prospective and Retrospective Memory Questionnaire; SD = standard deviation; tisa-cel = tisagenlecleucel.

of pain and fatigue and worsening of anxiety (measured with PROMIS-29) from baseline were not associated with disease response, CRS or neurotoxicity. Patient-reported toxicity monitoring (measured with PRO-CTCAE) revealed peaks of symptoms such as cough, decreased appetite, dry mouth, fatigue, hair loss, hand-foot syndrome, headache, nausea, problems with concentration, problems with memory at 14 days after CAR T-cell infusion followed by decline over time.[48]

A prospective cohort study of 27 NHL patients followed after axi-cel or tisa-cel infusion at Hopital Saint Louise (Paris, France), documented an improvement in self-reported prospective memory without any mid-term cognitive deterioration (measured by HADS and QMRD) between months 6 and 12 after CAR T-cell infusion.[50] However, anxiety and memory complaints (48% and 30% of patients, respectively) were more frequently reported at baseline CAR T-cell infusion than at the time of follow-up, and the frequency of anxiety (but not depression) was higher than in the general population.[50]

Profiles of self-reported symptom burden and functional impairments reported during the first 12 months after CAR T-cell therapy in a cohort of 60 patients who received axi-cel or tisa-cel at the University of Texas MD Anderson Cancer Center suggested that the period up to 90 days after CAR T-cell infusion was the most symptomatic period (internal group comparison of symptom burden according to the time from CAR T-cell infusion).[51] Fatigue-related symptoms (eg, fatigue, lack of energy, weakness in the arm and legs, and malaise) were the most severe symptoms reported at any time of PRO assessment.[51] Symptoms like fatigue, lack of appetite, weakness, inability to eat, and mood interference (as assessed with MDASI instruments) were less severe in patients who completed PRO assessment later than month 3 after infusion compared to those who completed PROs in the period between months 1 and 3.[51] Physical functioning impairment was worse in the first month after infusion compared to that reported from month 3 to 1 year after infusion (as measured with MDASI instruments and PROMIS-29)[51]. Patients who developed grade 2–4 CRS or neurotoxicity consistently reported more severe multiple symptom profiles compared with those who experienced grade 0–1 CRS or neurotoxicity after 1 month following CAR T-cell infusion (as measured with MDASI instruments and PROMIS-29).[51]

Ram et al[53] observed a transient increase in disability, worsening of symptoms, and emotional distress at 30 days after CAR T-cell infusion compared to baseline (before CAR T-cell infusion) in a matched control cohort study of 23 DLBC patients treated with axi-cel or tisa-cel. Improvement of overall health perception was found at 3 months after treatment infusion, as measured with the EORTC QLQ-C30. However, the paucity of PRO information (missing details on EORTC QLQ-C30 scale scoring and comparison) reported in the publication and the very small size of PRO sample hamper a critical appraisal of study findings.

Descriptive analysis of HRQoL patterns in 12 patients with various hematologic malignancies during the early timepoints after CAR T-cell infusion (up to month 3 after infusion) revealed clinically low physical well-being on day 7, and clinically low functional well-being from the day of CAR T-cell infusion up to month 1 (as measured with FACT-G).[55] Oswald et al reported mild fatigue perception from the day of CAR T-cell infusion up to month 1, mild interference pain interference only on day 14 after infusion, and impaired ability to participate in social role and activities between day 7 and month 1 after infusion (as measured with PROMIS-29).[55] The impairment level of physical function (as measured with PROMIS-29) was mild prior to CAR T-cell infusion, then changed to moderate from day 7 to month 1 after infusion and then returned to mildly impaired on month 2 after CAR T-cell therapy. FACT-G7 total scores revealed low HRQoL in the first week after CAR T-cell infusion.[55]

Among 118 NHL patients who received CAR T-cell at Moffitt Cancer Center (USA), longitudinal PRO assessment focused on patients' perception of cognition changes in the first year after CAR T-cell infusion revealed that only from month 3 to 1 year after CAR T-cell treatment patients reported worsening in global cognition and in the domains of memory, language, organization, and divided attention (as measured with Everyday Cognition Questionnaire).[56] Greater baseline fatigue, anxiety, and depression (as measured with the PROMIS-29) were associated with worse global cognition at month 3 after CAR T-cell infusion. In addition, patients with higher severity of neurotoxicity (ie, grade 2 or above) reported significantly worse cognition at 1-year timepoint compared to those with low grade neurotoxicity (ie, grade 0 or 1).[56]

DISCUSSION

We identified 14 CAR T-cell therapy studies on hematologic malignancies which have also evaluated PROs over the last 7 years. Despite substantial differences in study designs and patient populations, there seems to be evidence of improvements over time since CAR T-cell infusion in important aspects, such as physical functioning and fatigue. Notably, such improvements were observed using different PRO measures thereby lending further credit to the beneficial effects of CAR T-cell therapy. However, it should be noted that evidence of such improvements was mainly available from patients who responded to therapy. The most accurate information found in our review on this aspect was provided by Patrick et al[49] who reported PRO results of patients achieving a complete or partial response and those who did not achieve a complete or partial response or whose treatment response was not evaluable. More research is required to better understand HRQoL and symptoms trajectories by response to therapy.

While no comparative studies were identified in our review, we note that 2 works were published in recent weeks (hence just beyond the timeframe of our search) which provided novel insights on the relative value of CAR T-cell therapy compared to more traditional approaches.[59,60] Elsawy et al[59] compared axi-cel versus standard of care in patients with R/R LBCL in an RCT setting, and showed statistically and clinically meaningful improvements at days 100 and 150 for prespecified PRO endpoints which favored patients treated with axi-cel. However, these differences were substantially attenuated at later timepoints, resulting in similar HRQoL outcomes between treatment groups.[59] While it is possible that the lack of long-term HRQoL differences between treatment groups may simply depend on study-specific design issues, more evidence is needed from other comparative RCTs to better contextualize PRO improvements after CAR T-cell infusion in relation to standard treatments. Sidana et al[60], in a prospective observational study over a 6-month period, compared HRQoL and symptom burden of patients with mixed hematologic malignancies receiving CAR T-cell therapy to contemporary cohorts of patients receiving autologous SCT (auto-SCT) and allogeneic SCT (allo-SCT). Some key strengths of this study were that of having measured PROs already at 2 weeks after CAR T-cell infusion and showing that longitudinal collection of patient-reported symptoms with selected items from the PRO-CTCAE library is feasible in this setting. The authors found a short-term decline in HRQoL (nadired at week 2) in all 3 groups which then returned to baseline levels over time (ie, at 6 months). However, the decline in some key domains, such as physical well-being was significantly less with CAR-T versus auto-SCT or allo-SCT and returned to baseline faster. Furthermore, patients receiving CAR-T had fewer overall patient-reported AEs compared to patients who received auto-SCT and allo-SCT.[60]

Although we found 14 studies that provided PRO data, this may be a negligible number if put into the larger context of ongoing research in this area. Using clinical trial registry data (http://clinicaltrials.gov), Raymakers et al[61] examined 424 trials investigating CAR-T for the treatment of cancer (of which 76% were on patients with hematologic malignancies), and observed that only 29 (6.8%) included HRQoL as a primary or secondary outcome measure, suggesting that inclusion of PROs is still uncommon in CAR T-cell therapy research. As expected, considering the novelty of this therapy, many trials considered in their work (88.4%) were phase I or II trials,[61] and this may partly explain the lack of a more consistent use of PRO measures in ongoing trials. In our review half of the studies identified were indeed phase I or II trials.

The inclusion of PROs in early-phase trials of advanced cancer populations (as is typically the case for patients eligible for CAR T-cell therapy) may pose some challenges. However, evidence from other research settings including vulnerable hematologic populations, indicates that PRO assessment is feasible and can provide high-quality clinically relevant information.[62–65] Furthermore, it is known that in early-phase clinical trials, clinicians may underreport important symptomatic AEs of their patients,[66] thereby making the use of patients' self-reported symptoms a critical aspect to consider. For example, recent data support the use of the PRO-CTCAE already in phase I cancer trials to measure patient symptoms.[67] The PRO-CTCAE item library,[68] or other libraries such as the ones by the EORTC[69] and the FACIT,[70] are examples of valuable options to consider as they offer the opportunity to select specific validated items most relevant for a given research context. Of course, the selection of the most appropriate PRO assessment strategy should be guided by a specific research question and a combination of existing PRO validated questionnaires and ad-hoc items is also a valid option. A trend of improvement over time regarding the inclusion of PROs in early-phase cancer trials was recently observed,[71] and it is hoped this trend will continue considering the importance of the unique patient's perspective in the drug development process.[72] An advantage of including PRO measures in early-phase trials could also be that of using preliminary results to better inform the PRO design of later phase trials. Examples of the use of PRO measures in early-phase trials in vulnerable hematologic populations, and their implications, are available.[73,74]

Our review identified very limited evidence regarding patient experience during important phases of the disease trajectory. We found that only 4 and 5 studies provided information on PROs during the first 2 weeks from CAR T-cell infusion and during the long-term phase (ie, after the first year), respectively. Despite previous studies pointing to the importance of collecting long-term PRO data to identify symptoms or functional problems, which may only become evident several months or years after therapy,[75] our review indicates that major efforts are yet to be made in this direction. The integration of routine monitoring of PROs may be particularly relevant for patients who have received CAR T-cell therapy, for example, for collecting data on late toxicities. Given the logistics of CAR T-cell infusion, which typically requires patients to be treated and hospitalized in highly specialized centers and then return to their home local hospital, electronic (e)-PRO monitoring may be a valuable option.[44] For example, e-PROs monitoring via digital health tools may offer several advantages for these patients throughout the disease trajectory (including short-and long-term phases) as these may enhance physicians' ability to identify problems that require special attention. These tools may allow the triggering of alerts to clinicians based on predefined algorithms, thereby facilitating early identification of potentially clinically relevant problems.[76,77] Of course, the setting of these algorithms will have to consider several aspects, such as, the specific hematologic population, the timing of assessment during the disease trajectory, the type of PRO measure/s as well as other important features of the data collection infrastructure and available resources.

Remote monitoring systems in the CAR-T setting could also consider the collection of biometric parameters and vital signs in the acute care setting immediately after infusion, as preliminary data support the value of this approach, for example, to identify patients requiring expedited hospitalization.[78] The study by Oswald et al[55] identified in our review, also supported the feasibility of collecting biometric information via wearable devices (in addition to PROs) among patients with hematologic malignancies receiving CAR-T. Kenzik et al, reported

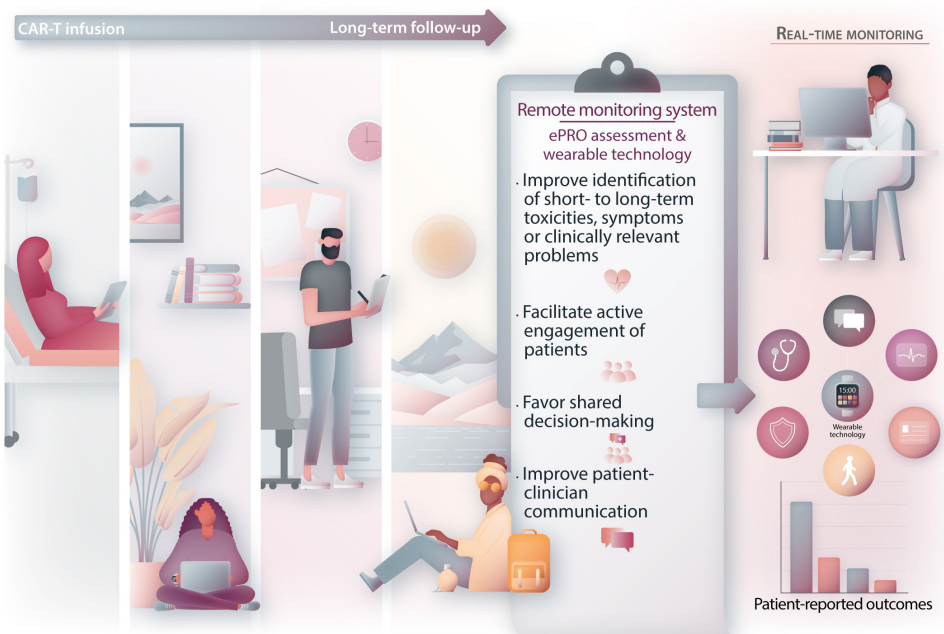

Figure 2. Descriptive illustration of a remote monitoring system approach combining both wearable technology and e-PRO assessment throughout the disease trajectory. PRO = patient-reported outcome.

that re-hospitalizations and emergency department visits after CAR-T are not uncommon during the first year, and this is particularly relevant within the first month after infusion.[79] Therefore, remote monitoring systems that include a combination of wearable technology and systematic e-PRO assessment may play a valuable role in improving healthcare delivery across all phases of the disease trajectory (see Figure 2, which also lists some potential advantages of this approach). In any case, we emphasize that future developments in this area should consider important digital health equity issues.[80] The recently published ESMO clinical practice guidelines on the use of PRO measures in cancer care, provide several high-quality recommendations, including the use of digital symptom monitoring via PROs.[81]

Previous studies have noted the importance of considering the implication of financial burden in patients receiving CAR-T[75]; however, we did not identify studies addressing this aspect. Indeed, in addition to the high costs associated with this therapy for healthcare systems, patients themselves may also report financial difficulties related, for example, to costs associated with follow-up visits or the management of toxicities. Cusatis et al[82] recently reported a qualitative and quantitative analysis suggesting that the financial impact of CAR T-cell therapy may increase over time, thereby emphasizing the importance of ensuring durable support to help patients face financial problems. There are now validated PRO measures that can be used to assess financial toxicity, for example, for the US cancer population,[83] and other PRO measures have been recently developed for patients living in countries with other types of healthcare systems.[84] Financial problems may differently affect patients depending on the specific country and type of healthcare system[85] and have been found to be associated with both HRQoL and survival outcomes.[86–88] Therefore, further research is needed to elucidate the implications of the financial burden on patients receiving CAR T-cell therapy.

Our review has limitations. Given the search strategy used, we may have provided limited evidence on specific areas of patient experience, for example, on neurocognitive problems. We did not include studies using performance-based measures (PBMs) to assess this aspect, while recent evidence indicates that PBMs may provide accurate information on cognitive problems (on top of the one generated via PRO measures) experienced by patients treated with CAR T-cell therapy,[89] and future work is needed to better understand the impact of CAR-T on potential neurocognitive deficits. Also, we did not evaluate the quality of PRO assessment methodology and outcome reporting and future research should focus on this important aspect. Although beyond the scope of our review, the HRQoL of caregivers of patients treated with CAR T-cell therapy may also be affected and this is a valuable area for further investigation.[90]

CONCLUSIONS

Current evidence seems to indicate that CAR T-cell therapy is associated with improved PROs (in selected domains) compared to baseline, at least in responding patients. This may suggest that AEs, while potentially severe, are also generally manageable and do not seem to substantially impact HRQoL after the acute phase. Some initial comparative data also indicate that, during the early phases after infusion, CAR T-cell therapy may be associated with a lower impact on HRQoL and symptom burden in relation to standard treatments.

These are reassuring results which have shown the added value of PRO assessment in CAR T-cell therapy research, but more evidence is needed from patients who did not respond to therapy and major efforts are also needed to address several unanswered questions. For example, future research will need to identify subgroups of patients for whom the effects of CAR-T on HRQoL may be more profound and long lasting. These may include patients with comorbidities, lower performance status at baseline, and more severe physical and psychosocial distress at baseline. These patients are frequently excluded from investigational trials. Real-world studies in which PRO measures are routinely assessed at baseline and at regular follow-up of all patients who receive CAR-T (regardless of response to therapy) will be able to better characterize these effects in more vulnerable populations. Also, HRQoL trajectories may vary depending on the hematologic population and there may be disease-specific issues. Patients with ALL may achieve complete or partial remission following CAR T-cell therapy but the risk of relapse is still high.[91] Hence, PRO measures could also be implemented in a more standardized way in the context of the model of integration of early palliative care with standard hematologic care as recently implemented for hematologic malignancies,[92–94] to more accurately engage patients in goals-of-care discussion, earlier in the disease course based on effective communication.[92]

The relationship between the financial burden experienced by these patients and HRQoL outcomes over the long-term period is also an important aspect that deserves special consideration. Remote monitoring systems including collection of e-PROs and other types of biometric data could potentially play a key role, and future research will have to elucidate the best practices to maximize their use across all phases of the disease trajectory.

AUTHOR CONTRIBUTIONS

FE and LC contributed to the study conception and design. FE, LC, FS, and JMG collected and assembled the data. All authors contributed in data interpretation, writing – original draft, and critically reviewed and approved the final version of the manuscript.

DISCLOSURES

FE has a consulting or advisory role: Amgen, AbbVie, Janssen, and Novartis. Research support (Institution) from AbbVie and Novartis outside the submitted work. FB has received travel grants and/or speaker honoraria from Pfizer, Celgene, Abbvie, Novartis, and Sanofi outside the submitted work. ML has been on the Advisory Boards for Novartis, Jazz Pharma, Sanofi, MSD, Abbvie, Daiichi-Sankyo, Gilead Sci, outside of the submitted work and has received a travel grant from Gilead Sci. MV reports honoraria from Amgen, Incyte, Novartis, Dephaforum Srl, Abbvie, and Astrazeneca and is on the advisory board for Amgen outside of the submitted work. UP reports honoraria from Gilead, BMS, and Novartis. All the other authors have no conflicts of interest to disclose.

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