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Longitudinal patient-reported outcomes in patients receiving chimeric antigen receptor T-cell therapy

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Key Points

- QOL and depression worsened soon after CAR-T, but QOL, psychological distress, and physical symptoms improved 6 months after CAR-T.
- A significant minority of patients report substantial persistent psychological distress and physical symptoms after CAR-T infusion.

Chimeric antigen receptor T-cell therapy (CAR-T) has transformed the treatment for relapsed/refractory hematologic malignancies; however, data on patient-reported outcomes in CAR-T are limited. We conducted a longitudinal study of adults with hematologic malignancies receiving CAR-T. We assessed quality of life (QOL; functional assessment of cancer therapy–general), psychological distress (hospital anxiety and depression scale, patient health questionnaire-9, posttraumatic stress disorder [PTSD] checklist), and physical symptoms (Edmonton symptom assessment scale–revised) at baseline, 1 week, 1, 3, and 6 months after CAR-T. We used linear mixed models to identify factors associated with QOL trajectory. We enrolled 103 of 142 eligible patients (3 did not receive CAR-T). QOL (B = 1.96; $P < .001$) and depression (B = −0.32; $P = .001$) worsened by 1 week and improved by 6 months after CAR-T. At 6 months, 18%, 22%, and 22% reported clinically significant depression, anxiety, and PTSD symptoms, respectively. At 1 week, 52% reported severe physical symptoms, declining to 28% at 6 months after CAR-T. In unadjusted linear mixed models, worse Eastern Cooperative Oncology Group performance status (B = 1.24; $P = .042$), receipt of tocilizumab (B = 1.54; $P = .042$), and receipt of corticosteroids for cytokine release syndrome and/or neurotoxicity (B = 2.05; $P = .006$) were associated with higher QOL trajectory. After CAR-T, QOL declined, and depression increased early, followed by improvements in QOL, psychological distress, and physical symptoms by 6 months after infusion. A significant minority of patients reported substantial psychological distress and physical symptoms longitudinally.

Introduction

Chimeric antigen receptor T-cell therapy (CAR-T) has revolutionized the treatment landscape for patients with hematologic malignancies.[1] Six CAR-T products have received Food and Drug

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The full-text version of this article contains a data supplement.

Administration approval, with many others in late phase clinical testing.[2-7] CAR-T has demonstrated durable remissions in ~40% of patients with aggressive lymphomas[3-5] and has prolonged progression-free survival among those with indolent lymphomas and multiple myeloma.[6-9]

However, patients receiving CAR-T often require a 2 or 3 week hospitalization because of potentially life-threatening toxicities, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which can result in immense physical and psychological symptoms.[10] Also, the majority of patients experience disease progression after CAR-T, yielding immense prognostic uncertainty and placing patients at risk of developing psychological distress.[11] Thus, patients receiving CAR-T are at risk for significant decline in quality of life (QOL) and increases in psychological distress and physical symptom burdens.

Despite this, evidence is lacking regarding the longitudinal QOL trajectory, psychological distress, and physical symptoms of patients receiving CAR-T. Previous studies have either evaluated a single CAR-T product[12,13] or included a single time point[14] or a small sample size of CAR-T recipients for comparing the outcomes with those of stem cell transplant recipients.[15] To date, only a few studies have assessed longitudinal patient-reported outcomes (PROs) in a broad array of CAR-T products and cancer diagnoses or evaluated factors associated with the QOL trajectory. Depicting the lived experience of patients receiving CAR-T and identifying factors associated with poor QOL are critical to guide the development of effective targeted supportive care interventions. Hence, this study aims to characterize longitudinal QOL, psychological distress, and physical symptoms in patients receiving CAR-T and determine the factors associated with the QOL trajectory.

Methods

Participants

Eligible patients were adults (age ≥18 years) with the ability to read questions in English who were given a referral to CAR-T for relapsed/refractory hematologic malignancies at the Massachusetts General Hospital (MGH) Cancer Center. We excluded patients with solid tumor malignancies (because of the lack of Food and Drug Administration–approved CAR-T products) and those with significant psychiatric or comorbid diseases, which the oncologist believed impaired their ability to provide informed consent.

Study design and procedures

We conducted a longitudinal study of consecutive patients who received a referral for CAR-T at MGH between April 2019 and November 2021. We used a systematic recruitment strategy that approached consecutively eligible patients for study participation. A research assistant obtained permission from the treating oncologist via email to approach the eligible patients. Willing participants provided written informed consent and completed the baseline questionnaires at the time of enrollment. We administered self-reported measures at the following time points: baseline (ie, any time between T-cell collection and admission for CAR-T infusion), 1 week after CAR-T infusion (±3 days), 1 month after CAR-T infusion (±1 week), 3 months after CAR-T infusion (±2 weeks), and 6 months after CAR-T infusion (±2 weeks). Patients who had disease progression or changed therapy due to lack of response continued in the study. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board.

Patient-reported measures

Sociodemographic and clinical characteristics. Patients completed a demographic questionnaire detailing their age, sex, race, ethnicity, marital status, income, religion, and educational level. We reviewed patients' electronic health records (EHRs) to obtain their cancer diagnosis, diagnosis date, CAR-T infusion date, CAR-T product use, Eastern Cooperative Oncology Group (ECOG) performance status, and bridging therapy use (yes vs no).

QOL. We used the functional assessment of cancer therapy–general (FACT-G) to assess patients' QOL at baseline and 1 week, 1 month, 3 months, and 6 months after CAR-T infusion. The FACT-G is a 27-item measure consisting 4 subscales that assess well-being across 4 domains (physical, functional, emotional, and social) during the preceding week. Scores range from 0 to 108, with higher scores indicating better QOL.[16]

Psychological distress. We used the hospital anxiety and depression scale (HADS) to assess participants' anxiety and depression symptoms at baseline and at 1 week, 1 month, 3 months, and 6 months after CAR-T infusion. The HADS is a 14-item questionnaire that contains 2 seven-item subscales assessing anxiety and depression symptoms during the preceding week and has demonstrated strong psychometric properties in oncology patient populations. Scores on each subscale range from 0 to 21, with a cutoff of 8 or greater denoting clinically significant anxiety or depression.[17] We also assessed major depressive symptoms, using the patient health questionnaire-9 (PHQ-9) at baseline and 1 week, 1 month, 3 months, and 6 months after CAR-T infusion. The PHQ-9 is a 9-item measure evaluating symptoms of major depressive disorder in accordance with the criteria of the diagnostic and statistical manual of mental disorders–IV.[18] The HADS subscales and PHQ-9 can also be evaluated continuously, with higher scores denoting worse psychological distress.[19]

We used a posttraumatic stress checklist (PCL) to evaluate the symptoms of posttraumatic stress at baseline and 1 month, 3 months, and 6 months after CAR-T infusion. The PCL is a 17-item measure that evaluates symptoms of posttraumatic stress disorder (PTSD) per the criteria of the diagnostic and statistical manual of mental disorders–IV. Higher scores on the PCL indicate worse PTSD symptoms, with a cutoff of 32 or greater denoting clinically significant PTSD symptoms.[20]

Physical symptom burden. We used a modified version of the self-administered revised Edmonton symptom assessment system to assess patients' symptoms. The Edmonton symptom assessment system assesses pain, fatigue, drowsiness, nausea, appetite, dyspnea, and well-being over the previous 24 hours.[21] We also included insomnia and trouble swallowing because these are prevalent symptoms in patients with cancer.[22,23] Individual symptoms are scored on a scale from 0 to 10, with 0 reflecting the absence of symptoms, and 10 reflecting the worst possible severity. Consistent with prior research, we categorized the

severity of the Edmonton symptom assessment system scores as none (0), mild (1-3), moderate (4-6), and severe (7-10).[24]

Clinical outcomes

We abstracted information about the patients' responses to CAR-T from the EHRs. For patients with the response not documented in the EHR, a board-certified oncologist (P.C.J.) evaluated the response based on imaging and laboratory data available in the medical record per the Lugano criteria for lymphoma[25,26] and International Myeloma Working Group uniform response criteria for multiple myeloma.[27] We also collected information regarding whether those with a response experienced disease progression (yes or no). We abstracted information about the incidence and grade of CRS and ICANS, use of tocilizumab for CRS, use of corticosteroids for CRS and/or ICANS management, hospital length of stay, hospital readmissions, and intensive care unit (ICU) admissions. CRS and ICANS were graded per the American Society for Transplantation and Cellular Therapy consensus criteria.[28] We determined the date of the last follow-up and the survival status (alive or deceased) via a review of the EHR. Patients receiving CAR-T were followed up closely at our institution and received the majority of their follow-up care at MGH. Outside records of outpatient visits and/or hospitalizations were acquired and relocated in the EHR.

Attrition and missing data

Overall, the missing data rates were 5%, 15%, 20%, and 28% at 1 week, 1 month, 3 months, and 6 months, respectively. The majority of the surveys (71%) were missing because of death or deterioration of health status.

Statistical analysis

We calculated descriptive statistics, including means or medians, for continuous variables, depending on the normality of the data and proportions for categorical variables. We determined the patients' best response achieved after CAR-T infusion and calculated the percentages of patients achieving complete response, partial response, very good partial response, stable disease, and progressive disease. We calculated the percentages of those experiencing CRS and ICANS and requiring tocilizumab and/or corticosteroids. We determined the rates of hospital readmission and ICU admission within 6 months of CAR-T infusion. We calculated the median follow-up time using the reverse Kaplan-Meier method. We translated depression (HADS), anxiety (HADS), and PTSD (PCL) symptoms into dichotomous outcomes that reflected the presence or absence of clinically significant symptoms. We calculated the percentage of patients experiencing clinically significant anxiety, depression, and PTSD symptoms at each time point. We determined the percentage of patients experiencing moderate and severe symptoms at each time point. We also determined the median and mean QOL scores for each time point. We calculated changes in the median QOL between baseline and 1 week; 1 week and 1 month; 1 month and 3 months; and 3 months and 6 months after CAR-T, with a change of at least 5 points on FACT-G considered clinically significant.[29] We computed linear mixed-effects models using maximum likelihood to account for missing data to characterize the trajectories of changes in patient outcomes (FACT-G, HADS, PHQ-9, and PCL). Analyses estimated the baseline values and rates of change separately for each outcome. Each model was constructed using random intercepts and slopes.

To identify the potential factors associated with pre–CAR-T QOL, we first tested the unadjusted associations between the following baseline variables of interest and pre–CAR-T QOL using linear regression models: age, sex, diagnosis, time since diagnosis, race, marital status, education level, income, ECOG performance status (analyzed as a continuous variable), bridging therapy use (yes vs no), and CAR-T product. Variables that were associated with pre–CAR-T QOL at $P < .10$ were then used to construct a multivariable linear regression model. We included sex in the multivariable model because of its known association with QOL.[30]

To identify potential factors associated with the QOL trajectory, we conducted unadjusted linear mixed models between the variables of interest and longitudinal QOL over time using an interaction term (factor × time): age, sex, diagnosis, time since diagnosis, race, marital status, education level, income, ECOG performance status (analyzed as a continuous outcome), bridging therapy use (yes vs no), CRS, ICANS, receipt of tocilizumab (yes vs no), receipt of corticosteroids for CRS and/or ICANS (yes vs no), and CAR-T product type.

Results

Patient participants

We enrolled 103 of 142 (72.5%) eligible patients who were scheduled to receive CAR-T. Among these patients, 100 went on to receive CAR-T (supplemental Figure 1). Table 1 describes the baseline characteristics of the patients (N = 100) in this study. The patients' median age was 66 years (range, 23-90 years), and most of them were male sex (63%), White (87%), married/living with a partner (77%), and college educated (74%). The most common diagnosis was lymphoma (71%), followed by multiple myeloma (28%), and B-cell acute lymphoblastic leukemia (1%). A plurality of patients received tisagenlecleucel (34%), followed by lisocabtagene maraleucel (16%), axicabtagene ciloleucel (13%), and idecabtaene vicleucel (12%). The vast majority (89%) of patients had an ECOG performance status of 0 or 1%, and 68% received bridging therapy. The median time from initial diagnosis to CAR-T infusion was 39.8 months (range, 3.9-258.3 months), and 59% of the patients received treatment during a clinical trial protocol.

Patient clinical outcomes

Table 2 summarizes clinical outcomes among patients. Among all patients (N = 100), 56% had a complete response, and 24% had either a partial response or very good partial response as their best response. Overall, 76% of the patients experienced CRS (50%, grade 1; 25%, grade 2; and 1%, grade 3+). Thirty-three percent of the patients experienced ICANS (14%, grade 1; 9%, grade 2; and 10%, grade 3+). Forty percent of the patients received corticosteroids for CRS and/or ICANS. Among all patients (N = 100), 41% had hospital readmission, and 9% had an ICU admission within 6 months of CAR-T infusion. The median length of stay was 14.5 days (range, 4-47 days) for CAR-T. With a median follow-up of 14.5 months (range, 0.4-36 months) from CAR-T infusion, 38% of the patients died.

Table 1. Patient characteristics

Clinical characteristics	Median (range) or N (%)
Age, median (range), y	66 (23-90)
Male sex	63
Race	
White	87
African American	2
Asian	1
American Indian or Alaska Native	1
Native Hawaiian or other Pacific Islander	1
Missing/not reported	4
Hispanic or Latino Ethnic group	6
Cancer diagnosis	
Lymphoma	71
Multiple myeloma	28
B-cell acute lymphoblastic leukemia	1
ECOG performance status	
0-1	89
2-4	6
Unknown	5
CAR-T product	
Tisagenlecleucel	34
Lisocabtagene maraleucel	16
Axicabtagene ciloleucel	13
Idecabtagene vicleucel	12
Brexucabtagene autoleucel	6
Ciltacabtagene autoleucel	3
Other	16
Religion	
Catholic	44
Other Christian	21
Jewish	2
Atheist	3
None	14
Other	6
Missing/not reported	4
Relationship status	
Married/living with a partner	77
Single	9
Divorced	5
Widowed	5
Noncohabiting relationship	2
Missing/not reported	2
Education	
High school or less	27
College	34
Beyond college	40
Missing/not reported	2
Received bridging therapy	68
Time since diagnosis, median (range), mo	39.8 (3.9-258.3)

Table 2. Outcomes

Clinical outcomes	Median (range) or N (%)
Best response to CAR-T	
CR	56
PR/VGPR	24
SD	5
PD	14
Not assessed	1
CRS	76
CRS grade	
1	50
2	25
3	0
4	1
5	0
ICANS	33
ICANS grade	
1	14
2	9
3	7
4	0
5	3
Received corticosteroids for CRS and/or ICANS	40
Follow-up time from CAR-T infusion, median (range), mo	14 (0.4-36)
Alive at the time of data cutoff	62
Index CAR-T hospitalization length of stay, median (range), d	14.5 (4-47)
Hospital readmission within 6 mo of CAR-T infusion	41
ICU admission within 6 mo of CAR-T infusion	9
Overall survival, median (range), mo	NR (95% CI, 20.3-NR)

CR, complete response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Longitudinal patient-reported QOL

Patients' QOL declined from baseline to 1 week during hospitalization for CAR-T, returned to baseline by 1 month, and improved by 3 and 6 months after CAR-T infusion (longitudinal model, B = 1.96; 95% confidence interval [CI], 1.23-2.68; $P < .001$; Figure 1). Specifically, the median QOL declined from a baseline of 77.9 to 70.0 1 week after CAR-T, then increased to 76.0 1 month after CAR-T, 83.5 3 months after CAR-T, and 83.7 6 months after CAR-T. All these changes exceeded the minimally important difference of 5 points in the FACT-G.[29]

Longitudinal patient-reported psychological distress

Similarly, patients' depression symptoms increased from baseline to 1 week during hospitalization for CAR-T, returned to near baseline by 1 month, and improved by 3 and 6 months after CAR-T infusion (HADS, B = −0.32; 95% CI, −0.50 to −0.13; $P = .001$; PHQ-9, B = −0.51; 95% CI, −0.77 to −0.25; $P < .001$; Figure 1).

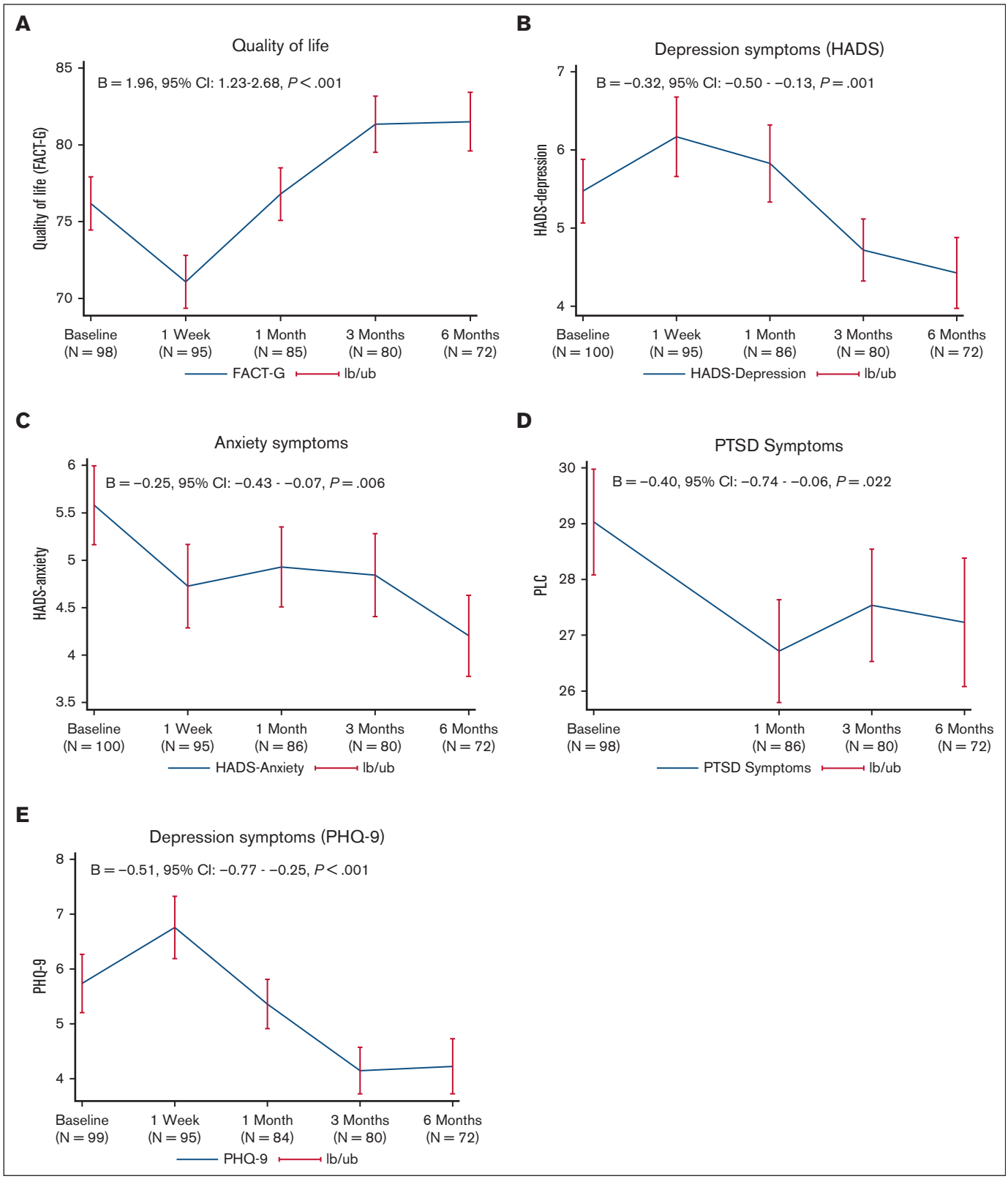

Figure 1. Longitudinal trajectory of PROs. (A) QOL; (B) depression symptoms (hospital anxiety and depression scale); (C) anxiety symptoms; (D) PTSD symptoms; and (E) depression symptoms (PHQ-9).

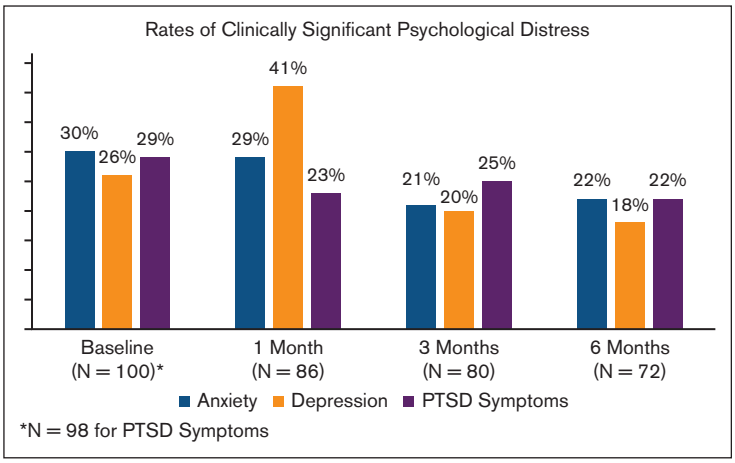

Figure 2. Rates of clinically significant psychological distress. The percentage of patients with clinically significant depression (hospital anxiety and depression scale), anxiety (hospital anxiety and depression scale), and PTSD (checklist) symptoms at each time point during CAR-T.

Anxiety (B = −0.25; 95% CI, −0.43 to −0.07; $P = .006$) and PTSD symptoms (B = −0.40; 95% CI, −0.74 to −0.06; $P = .022$) decreased from baseline to 1 month status after CAR-T infusion and remained at similar levels through months 3 and 6 after CAR-T infusion (Figure 1). Overall, 30 of 100 (30%) patients reported clinically significant anxiety at baseline, 25 of 86 (29%) at 1 month, 17 of 80 (21%) at 3 months, and 16 of 72 (22%) at 6 months (Figure 2). Additionally, 26 of 100 (26%), 35 of 86 (41%), 16 of 86 (20%), and 28 of 98 (29%) patients reported clinically significant depression symptoms at baseline and 1, 3, and 6 months after CAR-T, respectively. Among the patients, 28 of 98 (29%), 20 of 86 (23%), 20 of 80 (25%), and 16 of 72 (22%) reported clinically significant PTSD symptoms at baseline and 1, 3, and 6 months after CAR-T, respectively.

Longitudinal patient-reported physical symptoms

Seventy-eight of 98 (80%), 81 of 94 (86%), 64 of 86 (75%), 58 of 80 (73%), and 48 of 72 (67%) of the patients reported moderate or severe physical symptoms at baseline, 1 week, and 1, 3, and 6 months after CAR-T, respectively. Additionally, 46 of 98 (47%), 49 of 94 (52%), 30 of 86 (35%), 22 of 80 (28%), and 20 of 72 (28%) patients reported severe symptoms at baseline, 1 week, and 1, 3, and 6 months after CAR-T, respectively. (Figure 3).

Factors associated with patient-reported QOL

In unadjusted linear regression analyses, older age (B = 0.54; 95% CI, 0.26-0.82; $P < .001$), college education (7.91; 95% CI, 1.06-14.7; $P = .024$), and higher income (B = 7.94; 95% CI, 0.88-15.0; $P = .028$) were significantly associated with better pre–CAR-T QOL (Table 3), whereas bridging therapy use (B = −8.99; 95% CI, −16.2 to −1.82; $P = .015$) and worse ECOG performance status (B = −9.91; 95% CI, −15.4 to −4.46; $P < .001$), were associated with worse pre–CAR-T QOL. Sex, marital status, race, diagnosis, time since diagnosis, and CAR-T product type were not associated with pre–CAR-T QOL in any way (Table 3). In a multivariable linear regression model including age, sex, education level, income, ECOG performance status, and bridging therapy use, worse ECOG performance status (B = −7.09; 95% CI, −12.9 to −1.32; $P = .017$) was associated with worse pre–CAR-T QOL; bridging therapy use (B = −7.25; 95% CI, −14.9 to 0.39; $P = .063$) was associated with worse pre–CAR-T QOL, whereas older age (B = 0.31; 95% CI, −0.02 to 0.64; $P = .067$) was associated with better pre–CAR-T QOL, but these associations were not statistically significant (Table 4).

In separate unadjusted linear mixed models, worse pre–CAR-T ECOG performance status (B = 1.24; 95% CI, 0.04-2.43; $P = .042$), receipt of tocilizumab (B = 1.54; 95% CI, 0.06-3.02; $P = .042$), and receipt of corticosteroids for CRS and/or ICANS (B = 2.05, 95% CI, 0.60-3.51; $P = .006$) were all associated with a higher longitudinal QOL trajectory. No other factors were significantly associated with the longitudinal QOL trajectory (Table 5).

Discussion

In this study, we examined the longitudinal PROs of patients receiving CAR-T. We demonstrated that these patients experienced a deterioration of QOL and an increase in depression symptoms and severe physical symptoms during the early period after CAR-T. However, by months 3 and 6 after CAR-T infusion, we

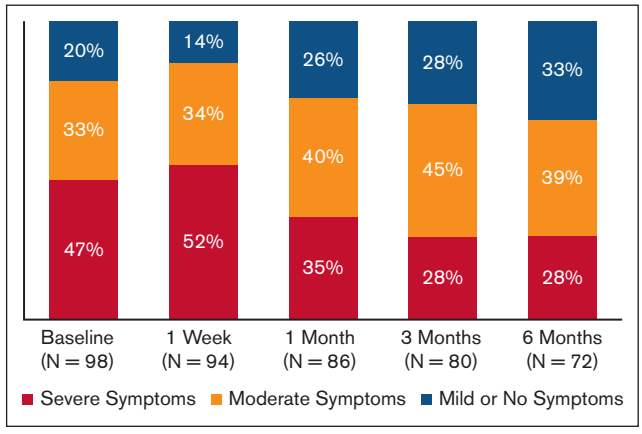

Figure 3. Longitudinal physical symptom burden. The percentage of patients with mild or no symptoms, moderate symptoms, or severe symptoms on the Edmonton symptom assessment scale–revised instrument at each time point during CAR-T.

Table 3. Univariate factors associated with pre–CAR-T QOL

Variable	β (95% CI)	Standard error	*P* value
Age (y)	0.54 (0.26-0.82)	0.14	< .001
Female sex	−1.48 (−8.61 to 5.65)	3.59	.682
Married/with a partner	6.51(−1.80 to 14.8)	4.18	.123
College educated	**7.91 (1.06-14.7)**	**3.45**	**.024**
Income ≥ $100 000	**7.94 (0.88-15.0)**	**3.55**	**.028**
White race	6.96 (−3.44 to 17.4)	5.24	.187
Bridging therapy use	**−8.99 (−16.2 to −1.82)**	**3.61**	**.015**
ECOG performance status	**−9.91 (−15.4 to −4.46)**	**2.74**	**< .001**
Diagnosis of lymphoma/leukemia	3.80 (−3.78 to 11.4)	3.82	.322
Months since diagnosis	−0.04 (−0.11 to 0.03)	0.03	.236
CAR-T product			
B-cell maturation antigen CAR-T (ref)	Ref	Ref	Ref
Tisa-cel	0.06 (−8.72 to 8.83)	4.42	.990
Axi-cel or Brexu-cel	8.37 (−1.71 to 18.4)	5.07	.102
Liso-cel	6.21 (−4.42 to 16.8)	5.35	.249

Ref., reference.
β-weights indicate differences in FACT-G QOL score based on each univariate predictor. Bolded values are for those with a P value < 0.05.

observed an improvement in QOL, depression symptoms, and severe physical symptoms. Additionally, anxiety and PTSD symptoms declined over time. These results highlight the severity of QOL deterioration, psychological distress, and physical symptom burden experienced by CAR-T recipients during acute treatment but demonstrate that CAR-T ameliorates patients' QOL and physical and psychological symptom impairments during the recovery phase.

We described the QOL deterioration, psychological distress, and physical symptoms experienced longitudinally by patients receiving CAR-T. Patients had a statistically significant decline in QOL and an increase in depressive symptoms by week 1 after CAR-T infusion. Six months after CAR-T infusion, patients reported statistically significant improvements in QOL as well as in psychological distress and physical symptoms. The mean QOL of CAR-T recipients was significantly lower than that of the US general adult population at baseline and 1 week after CAR-T infusion, but by 3 and 6 months after CAR-T, QOL was no different from that of the US general adult population.[31]

The small sample size and high death rate of nonresponders limited our ability to further evaluate the mechanism of the impact of CAR-T on PROs. At 6 months after CAR-T, the QOL of nonresponders was numerically less than that of responders, although this finding was not statistically significant in the setting of a small sample size of nonresponders. Thus, we hypothesized that our findings are likely explained by the impact of CAR-T on ameliorating cancer-related symptoms in this population with relapsed/refractory disease and a known high symptom burden.[15,32,33] Prior studies focusing on single CAR-T products have also shown sustained improvements in QOL beginning around 1 to 3 months after CAR-T.[12,13,15,32,33] This study adds to the literature by examining longitudinal QOL as well as psychological distress and symptom burden in a cohort of patients encompassing a variety of diagnoses and CAR-T products. Our findings demonstrate the effectiveness of CAR-T in ameliorating disease-related QOL and physical and psychological symptom impairments, likely through improved disease control.

Importantly, although overall QOL, psychological distress, and physical symptoms improved over time, a significant minority of

Table 4. Multivariable analysis of factors associated with pre–CAR-T QOL

Variable	β (95% CI)	Standard error	*P* value
Age (y)	0.31 (−0.02 to 0.64)	0.17	.067
Female sex	−4.55 (−11.7 to 2.61)	3.60	.209
College educated	3.86 (−3.86 to 11.6)	3.88	.322
Income ≥ $100 000	4.14 (−3.33 to 11.6)	3.75	.273
ECOG performance status	**−7.09 (−12.9 to −1.32)**	**2.89**	**.017**
Bridging therapy use	−7.25 (−14.9 to 0.39)	3.84	.063

β-weights indicate differences in FACT-G QOL score based on each predictor. Bolded values are for those with a P value < 0.05.

Table 5. Univariate factors associated with longitudinal QOL (time × factor interaction)

Variable	β (95% CI)	Standard error	*P* value
Age (y)	−0.03 (−0.09 to 0.04)	0.03	.435
Female sex	0.40 (−10.8 to 3.82)	3.73	.349
Married/with a partner	−0.06 (−1.79 to 1.66)	0.88	.944
College educated	0.01 (−1.48 to 1.49)	0.76	.992
Income ≥$100 000	−0.74 (−2.35 to 0.87)	0.82	.369
White race	−0.85 (−3.10 to 1.40)	1.15	.460
Bridging therapy use	0.67 (−0.87 to 2.20)	0.78	.395
ECOG performance status	**1.24 (0.04-2.43)**	**0.61**	**.042**
Diagnosis of lymphoma/leukemia	−0.93 (−2.48 to 0.62)	0.79	.238
Months since diagnosis	0.00 (−0.01 to 0.02)	0.01	.602
CAR-T Product			
BCMA CAR-T (ref)	Ref	Ref	Ref
Tisa-cel	0.56 (−8.64 to 9.76)	4.70	.905
Axi-cel or Brexu-cel	5.84 (−4.71 to 16.4)	5.39	.278
Liso-cel	7.57 (−3.58 to 18.7)	5.69	.183
CRS	0.06 (−1.65 to 1.76)	0.87	.948
Immune effector cell-associated neurologic toxicity syndrome	0.97 (−0.62 to 2.57)	0.81	.231
Receipt of tocilizumab	**1.54 (0.06-3.02)**	**0.76**	**.042**
Receipt of corticosteroids	**2.05 (0.60-3.51)**	**0.74**	**.006**

β-weights indicate differences in FACT-G QOL score based on each univariate predictor. Bolded values are for those with a P value < 0.05.

patients reported psychological distress 6 months after CAR-T infusion, with approximately one-fifth reporting clinically significant anxiety, depression, and/or PTSD symptoms. Remarkably, more than half of the patients reported severe physical symptoms in the first week after CAR-T infusion. Moreover, more than a quarter of patients noted severe physical symptoms 6 months after CAR-T infusion, with more than two-thirds of patients noting moderate or severe physical symptoms. These results underscore the need for supportive care interventions to improve the QOL, psychological distress, and physical symptoms experienced by patients receiving CAR-T during and after treatment. In a randomized controlled trial of hematopoietic stem cell transplant recipients, an integrated palliative care intervention resulted in clinically significant improvements in patients' QOL, symptom burden, and psychological distress.[34] Importantly, patients receiving palliative care had sustained improvements in psychological distress symptoms at 3 and 6 months after receiving hematopoietic stem cell transplant compared with those receiving usual care.[35] Therefore, integrated palliative care interventions could represent a promising strategy for improving PROs in patients receiving CAR-T and should be evaluated in future studies.

We also assessed the factors associated with pre–CAR-T QOL and longitudinal QOL trajectory in patients receiving CAR-T. We identified worse pre–CAR-T ECOG performance as a factor associated with lower pre–CAR-T QOL, and worse pre–CAR-T ECOG performance status, receipt of tocilizumab, and receipt of corticosteroids for CAR-T toxicities as factors associated with a higher longitudinal QOL trajectories. To our knowledge, this is the first study to evaluate factors associated with the QOL trajectory in patients receiving CAR-T. ECOG performance status has been identified as a factor associated with QOL in other populations with cancer,[36] and patients with worse pre–CAR-T performance status secondary to disease may experience a relatively larger improvement in their QOL with improved disease control. Tocilizumab, an interleukin 6 receptor antagonist,[37] and corticosteroid use were both associated with a higher longitudinal QOL. The mechanism for these findings is unclear, although it is conceivable that more aggressive management of CRS and/or ICANS led to an improved longitudinal QOL trajectory over the study period. Additionally, prior work has demonstrated an association between interleukin 6 and higher rates of depression.[38] Thus, future studies could further examine the relationship between interleukin 6 and QOL in CAR-T recipients and whether tocilizumab may affect the QOL trajectory in this patient population. Interestingly, diagnosis was not associated with the QOL trajectory, despite the differences in disease biology and management between lymphomas, acute lymphoblastic leukemia, and multiple myeloma. The latter finding suggests that CAR-T has a relatively similar impact on PROs across relapsed/refractory hematologic malignancies. Future studies should continue to explore the factors associated with QOL across diseases and lines of therapy. By determining factors associated with the QOL trajectory, these findings can help clinicians conduct shared decision-making with patients and identify populations who are at risk and may benefit from supportive care interventions designed to optimize QOL and symptom burden during treatment.

Several limitations of this study are worth considering. Firstly, our study evaluated patients at a single large academic center who were predominantly White, married, and college educated, which might have limited the generalizability of our findings. Secondly, our study had attrition from a subset of patients, mostly because of

death from disease progression; thus, our findings might have underestimated the rates of QOL decline, psychological distress, and physical symptom burden, particularly in this population. Thirdly, our sample size limited our ability to examine the differences in cellular therapy products. Fourthly, our study did not include a 2 week post-CAR-T infusion time point, which might have resulted in an underestimation of patient-reported symptoms, given that some cellular therapy products have toxicities that often peak around this time. Future work should examine PROs in cohorts with greater racial and socioeconomic diversity and examine the QOL trajectory among larger sample sizes of different cellular therapy products.

Conclusions

We depicted the longitudinal PROs of patients with relapsed/refractory hematologic malignancies, demonstrating a decline in QOL and an increase in depression symptoms early in treatment, followed by an improvement in QOL, psychological distress, and physical symptom burden 3 and 6 months after CAR-T infusion. A significant minority of patients report substantial psychological and physical symptom burdens throughout the treatment trajectory. Our findings highlight the ability of CAR-T to improve PROs and the unmet need for supportive care interventions to ameliorate the QOL, psychological distress, and physical symptoms throughout the continuum of patient experience.

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Authorship

Contribution: P.C.J. and A.E.-J. designed the study; M.W.L., D.V., and K.K. collected data; P.C.J. and A.E.-J. performed the statistical analyses, analyzed and interpreted the data; and wrote the manuscript; and all authors were involved in revising the manuscript critically for important intellectual content, provided final approval for the manuscript, and agreed to be accountable for all aspects of the work.

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