Quality of life in patients with beta-thalassemia: a prospective study of transfusion-dependent and non-transfusion-dependent patients in Greece, Italy, Lebanon, and Thailand

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β-thalassemias are a group of genetic disorders characterized by reduced levels of functional hemoglobin (Hb).[1] The prognosis of patients with β-thalassemia has improved markedly in recent years owing to the availability of red blood cell (RBC) transfusion and iron chelation therapy (ICT). Survival of patients who have been regularly transfused and treated with appropriate ICT now extends beyond 40 years of age.[2]

Despite important improvements in patient survival, the burden of regular therapy poses a negative impact on patients' quality of life (QoL). Patients with β-thalassemia who require regular and lifelong RBC transfusions to treat the disease are generally categorized as having transfusion-dependent thalassemia (TDT); non-transfusion-dependent thalassemia (NTDT) patients may only require occasional transfusions. Regular transfusions and associated complications including iron overload have a significant impact on the QoL of adult TDT patients.[3] NTDT patients also experience significant impacts on their QoL due to their disease, often associated with iron overload and the difficulty of adhering to ICT.[4]

As a result, health-related QoL has emerged as a key focus of comprehensive clinical care in patients with β-thalassemia. Understanding the degree of patient-perceived health impairment is essential to determine the burden of illness of β-thalassemia and to recommend suitable therapy. The objective of this study was to document the burden of illness (defined as impairment of QoL) in NTDT and TDT patients receiving standard of care with a focus on patient-reported physical and mental health QoL domains.

A multisite, prospective, non-interventional observational study of adult patients with β-thalassemia was conducted at 5 treatment centers in 4 countries: Greece (1), Italy (1), Lebanon

(1), and Thailand (2). Eligible patients were aged > 18 years, could read and speak the official local language, had a diagnosis of β-thalassemia or Hb E/β-thalassemia and Eastern Cooperative Oncology Group performance status score of 0 to 1, and were willing to give informed consent to provide self-reported QoL measurements. Patients were divided into 2 cohorts according to their level of transfusion dependence during the 24 weeks prior to study entry. Participants who received ≥ 6 RBC units and had no transfusion-free period for ≥ 35 days were classified as having TDT. Participants who received ≤ 5 RBC units were classified as having NTDT. For the NTDT cohort, participants were included if their most recent Hb level was ≤ 10 g/dL. QoL outcomes were collected using 2 validated PRO instruments, the 36-Item Short Form Survey version 2.0 (SF-36v2) and the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaires. Data were collected at baseline and then once every 3 weeks for up to 24 weeks (up to 9 time points). The primary endpoints were the 2 summary scores of the SF-36v2, the Physical Component Score and Mental Component Score, for all patients with β-thalassemia over the study period compared with the general population. Secondary endpoints included changes in SF-36v2 and FACT-An scores between TDT and NTDT patients over the study period. Additional details regarding the methods used can be found online in the Supporting Information section.

A total of 102 patients with β-thalassemia were screened. Among them, 99 patients (TDT, *n* = 49 [49.5%] and NTDT, *n* = 50 [50.5%]) were eligible and participated in the study between March 2016 and January 2017. Baseline measurements were completed for all patients except 2 TDT patients who did not complete the SF-36v2 and FACT-An questionnaires at baseline. At 24 weeks, collection of QoL outcomes was completed for 36 NTDT and 17 TDT patients.

The mean age of all patients with β-thalassemia was 31.6 years (standard deviation [SD], 10.4) and 69 (69.7%) patients were female (Supporting Information Table 1). The mean (SD) time since initial diagnosis was 24.8 years (11.4); this was longer for TDT than for NTDT patients (28.0 [10.4] vs 21.8 [11.5] years). At screening, mean (SD) Hb level was 8.2 g/dL (1.2) in NTDT patients and 8.8 g/dL (1.5) in TDT patients. Overall, 52.5% of patients had a history of clinically significant iron overload; this was more common in TDT patients compared with NTDT patients (75.5 vs 30.0%). Consequently, ICT at baseline was used more frequently in TDT patients (85.7%) compared with NTDT patients (24.0%).

At baseline, mean SF-36v2 General Health score was lower for patients with β-thalassemia than for the general population (T-scores < 47), indicating worse QoL (Supporting Information Table 2). Mean SF-36v2 scores for NTDT patients were lower for all domains and summary scores than for TDT patients, except for Role-Physical (Table). Mean (SD) differences between NTDT and TDT patients were clinically meaningful and reached, or were close to reaching the statistical significance level of 0.01 for the Mental Component Score (47.4 [8.4] vs 51.6 [7.2], $P < 0.01$), and the domains of General Health, (41.9 [8.2] vs 46.3 [10.0]; $P = 0.018$), Vitality (49.8 [8.1] vs 54.0 [7.1]; $P = 0.008$), and Mental Health (47.8 [7.8] vs 51.7 [6.9]; $P = 0.011$).

NTDT patients reported lower QoL scores than TDT patients on all domains of the FACT-An questionnaire (Table). Statistically significant differences were observed between NTDT and TDT patients for FACT-General (83.0 [11.3] vs 89.0 [10.7]; $P = 0.009$), and Functional Well-Being (20.1 [4.2] vs 23.0 [3.9]; $P < 0.001$), indicating worse QoL in NTDT patients.

Mean and median decreases from baseline to Week 24 for patients with β-thalassemia were observed in the SF-36v2 Mental Health domain and the Physical Component Scores, indicating that QoL deteriorated over the study period (Supporting Information Table 3). Patients with β-thalassemia experienced decreased QoL scores over the study period in 7 of the 12 FACT-An domains (Functional Well-Being, Social and Family Well-Being, Trial Outcome Index, FACT-An Total Score, FACT-General Total Score, Anemia Subscale, Fatigue Symptoms), indicating worse QoL at the end of the study. Mean change over 24 weeks was statistically significant for the Functional Well-Being domain (mean [SD] change −2.2 [4.0]; median change [Q1;Q3] −2.0 [−5.0, 0.0]; $P < 0.001$) and the FACT-General Total Score (mean [SD] change −4.7 [11.8]; median change [Q1;Q3] −4.0 [−12.0, 3.0]; $P = 0.005$) (Supporting Information Table 3).

Compared with TDT patients, NTDT patients had, in general, less favorable changes in QoL over the 24 weeks of the study. They experienced reductions in the SF-36v2 Role-Physical and Mental Health domain scores. Both component scores indicated impaired QoL, while TDT patients had maintained or slightly improved QoL. The difference in change from baseline to Week 24 in the SF-36v2 Role-Physical scores between NTDT and TDT patients was statistically significant (mean change [SD] −4.1 [9.2] vs 4.1 (8.4); $P = 0.003$ (Supporting Information Table 4). Decreased FACT-An scores were observed in NTDT patients for the Emotional Well-Being, FACT-An Total Score, Anemia Subscale, Fatigue Symptoms, Fatigue Impact, Fatigue Experience, and Trial Outcome Index whereas TDT patients experienced a smaller deterioration, maintained or improved QoL in these domains. No significant differences were observed between the NTDT and TDT patients in terms of changes in FACT-An score from baseline to Week 24 (Supporting Information Table 4).

This study demonstrates the burden of disease for patients with β-thalassemia, and highlights observed differences in QoL between NTDT and TDT patients. In the routine clinical care setting, NTDT patients generally reported worse QoL across most domains of the SF-36v2, indicating that TDT patients have a higher level of functioning than NTDT patients. Clinically meaningful differences were observed for the SF-36v2 Mental Component Score, and General Health, Vitality, and Mental Health domains, and FACT-An Functional Well-Being, and the FACT-General Total Score. After 24 weeks of follow-up, changes from baseline in SF-36v2 Role-Physical scores were significantly different between NTDT and TDT patients; NTDT patients experienced impaired QoL while TDT patients had maintained or slightly improved QoL. These results suggest that while NTDT patients may not require regular transfusions, they may experience a significant reduction in functional outcomes.

The results of this study are generally aligned with results reported in the few published studies of QoL in patients with β-thalassemia. In Sobota et al. (2011), data from the Thalassemia Longitudinal Cohort of the Thalassemia Clinical Research Network is reported.[5] In that study, patients with β-thalassemia in the USA and UK had lower scores on 7 out of 8 domains of the SF-36 compared with general population benchmarks; in our study, General Health was the only domain in which patients with β-thalassemia reported worse QoL than the general population. However, NTDT patients had greater QoL impairment compared with TDT patients. This is consistent with the Intercontinental Collaborative Study conducted in TDT and NTDT patients in Canada, Lebanon, and Iran, in which NTDT patients experienced significant reductions in QoL, as measured by SF-36, compared with TDT patients.[6]

In summary, critical unmet medical needs remain for NTDT patients as they experience poorer QoL compared with TDT patients. There is a need for new PRO instruments to accurately measure reductions in QoL in NTDT patients, as well as new interventions to treat these patients to reduce their unique burden of disease. Development of a new, validated PRO instrument, to assess the severity of symptoms in NTDT patients specifically is currently underway.

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CONFLICT OF INTEREST

MDC is a board member for Bluebird, Celgene Corporation, CRISPR, La Jolla, Novartis, Protagonist, and Sanofi/Genzyme. AK has received research support from, and is an advisory and educational board member of, Apopharma, Celgene Corporation, and Novartis. VV has received research support from Bio-Rad, Celgene Corporation, Novartis, Roche, and SEBIA,. PS has received research support from Celgene Corporation and Novartis. JP, AL, and VJC are employees of Celgene Corporation. AT has received honoraria and research funding from Novartis, and research funding from Celgene Corporation and Roche.

AUTHOR CONTRIBUTION

MDC and AT designed the research study. MDC, AK, VV, PS, and AT conducted the study. JP, AL, and VJC performed the analyses. All authors interpreted the data, offered critical review of the manuscript, and approved the manuscript.

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TABLE Mean differences in QoL scores between NTDT and TDT patients at baseline

SF-36v2				
Domain / component scores	**NTDT patients (*n* = 50) mean (SD)**	**TDT patients (*n* = 49) mean (SD)**	**Difference between NTDT and TDT patients**	
			Mean difference (SD)	***P* value (t-test)**
Physical Functioning	50.2 (6.1)	51.1 (5.6)	−0.9	0.446
Role-Physical	49.8 (6.4)	48.5 (6.8)	1.3	0.323
Bodily Pain	52.5 (9.2)	55.2 (6.8)	−2.7	0.108
General Health	41.9 (8.2)	46.3 (10.0)	−4.4	0.018*
Physical Component Score	49.7 (6.5)	50.3 (5.9)	−0.6	0.632
Vitality	49.8 (8.1)	54.0 (7.1)	−4.2	0.008*
Social Functioning	48.7 (7.7)	50.7 (6.9)	−2.0	0.177
Role-Emotional	47.7 (7.9)	50.3 (7.4)	−2.6	0.092
Mental Health	47.8 (7.8)	51.7 (6.9)	−3.9	0.011*
Mental Component Score	47.4 (8.4)	51.6 (7.2)	−4.2	0.009*

FACT-An			
Scales / domains	**NTD patients (*n* = 50)**	**TDT patients**	**Difference between NTDT and TDT patients**

	Mean (SD)	(*n* = 49) Mean (SD)	Mean difference (SD)	*P* value
Physical Well-Being (k = 7)	23.0 (3.7)	23.9 (3.0)	−0.9	0.197
Social and Family Well-Being (k = 7)	21.4 (4.3)	22.1 (4.5)	−0.7	0.426
Emotional Well-Being (k = 6)	18.6 (3.3)	19.9 (2.8)	−1.4	0.030
Functional Well-Being (k = 7)	20.1 (4.2)	23.0 (3.9)	−3.0	≤ 0.001*
FACT-General (k = 27)	83.0 (11.3)	89.0 (10.7)	−6.0	0.009*
FACT-An Anemia Symptoms (k = 7)	21.7 (3.1)	22.4 (2.8)	−0.7	0.224
Fatigue Symptoms (k = 13)	38.3 (9.0)	40.8 (5.4)	−2.5	0.104

* Denotes statistical significance.

FACT, Functional Assessment of Cancer Therapy; FACT-An, Functional Assessment of Cancer Therapy-Anemia; k, the number of items in a scale/domain; *n*, number; NTDT, non-transfusion dependent thalassemia; SD, standard deviation; SF-36v2, 36-Item Short Form Survey version 2; TDT, transfusion dependent thalassemia.