ASBMT
American Society for Blood and Marrow Transplantation

Prospective Assessment of Health-Related Quality of Life in Pediatric Patients with Beta-Thalassemia following Hematopoietic Stem Cell Transplantation

Giovanni Caocci,[1] Fabio Efficace,[2] Francesca Ciotti,[3] Maria Grazia Roncarolo,[3] Adriana Vacca,[1] Eugenia Piras,[1] Roberto Littera,[1] Raji Suleiman Dawood Markous,[4] Gary Stephen Collins,[5] Fabio Ciceri,[3] Franco Mandelli,[2] Sarah Marktel,[3] Giorgio La Nasa[1,6]

Although hematopoietic stem cell transplantation (HSCT) has been widely used to treat pediatric patients with beta-thalassemia major, evidence showing whether this treatment improves health-related quality of life (HRQoL) is lacking. We used child-self and parent-proxy reports to prospectively evaluate HRQoL in 28 children with beta-thalassemia from Middle Eastern countries who underwent allogeneic HSCT in Italy. The PedsQL 4.0 Generic Core Scales were administered to patients and their parents 1 month before and 3, 6, and 18 months after transplantation. Two-year overall survival, thalassemia-free survival, mortality, and rejection were 89.3%, 78.6%, 10.9% and 14.3%, respectively. The cumulative incidence of acute and chronic graft-versus-host disease (GVHD) was 36% and 18%, respectively. Physical functioning declined significantly from baseline to 3 months after HSCT (median PedsQL score, 81.3 vs 62.5; $P = .02$), but then increased significantly up to 18 months after HSCT (median score, 93.7; $P = .04$). Agreement between child-self and parent-proxy ratings was high. Chronic GVHD was the most significant factor associated with lower HRQoL scores over time ($P = .02$). The child-self and parent-proxy reports showed improved HRQoL in the children with beta-thalassemia after HSCT. Overall, our study provides preliminary evidence-based data to further support clinical decision making in this area.

Biol Blood Marrow Transplant 17: 861-866 (2011) © *2011 American Society for Blood and Marrow Transplantation*

KEY WORDS: Child self-report, Parent-proxy report, Pediatric Quality of Life Inventory

INTRODUCTION

The many advances in the treatment of patients with beta-thalassemia major have dramatically inproved survival rates over the past decade [1,2]. Nevertheless, several problems continue to hamper the management of this chronic disease, including poor compliance with iron chelation therapy, endocrine problems, the high frequency of chronic hepatitis C, and the psychosocial morbidity associated with chronic disease [3]. Children suffering from this serious life-limiting and potentially life-threatening condition report a substantial reduction of social relationships and an overall sense of isolation [4]. Allogeneic hematopoietic stem cell transplantation (HSCT) from an HLA-matched donor remains the only potential cure [5]. Unfortunately, this procedure is burdened by a variable incidence (6%-30%) of transplantation-related mortality (TRM), depending on the pretransplantation risk stratification according to Lucarelli et al. [6]. Acute and chronic graft-versus-host disease (GVHD) are frequent complications and contribute significantly to the risk of TRM [7,8]. Moreover, the posttransplantation phase is associated with increased clinical and laboratory tests, frequent hospital admissions for infections, adverse drug effects, and GVHD-related complications, all of which contribute to significant impairment of health-related quality of life (HRQoL).

HRQoL is generally conceptualized as a multidimensional construct referring to patients' perceptions of the impact of disease and treatment on their physical, psychological, and social functioning and well being [9-11]. Despite the worldwide diffusion of

From the [1]Bone Marrow Transplant Center, R. Binaghi Hospital, Cagliari, Italy; [2]Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases Data Center, Rome, Italy; [3]Pediatric Immuno-Hematology and BMT Unit, IRCCS San Raffaele Hospital, Milan, Italy; [4]Thalassemia Center, Hevi Pediatric Hospital, Duhok, Iraq; [5]Centre for Statistics in Medicine, University of Oxford, Oxford, UK; and [6]Department of Hematology, University of Cagliari, Cagliari, Italy.

Financial disclosure: See Acknowledgments on page 866.

Correspondence and reprint requests: Dr Giovanni Caocci, Centro Trapianti di Midollo Osseo, P.O. "R. Binaghi," Via Is Guadazzonis, 3 09126 Cagliari, Italy (e-mail: gcaocci@alice.it).

Received July 14, 2010; accepted September 8, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.09.011

thalassemia and its high incidence in developing countries (the Mediterranean area, Middle East, and Asia), HRQoL has been investigated only rarely [12-16]. In fact, the literature contains only two studies on the HRQoL of thalassemia patients after HSCT [17,18]. In the first of these studies, good HRQoL outcomes were obtained in a cohort of 19 adult thalassaemia patients who received a transplant from an HLA-matched unrelated donor [17]. More recently, Cheuk et al. [18] investigated HRQoL in 21 thalassemia patients who underwent allogeneic HSCT from HLA-matched sibling donors and found that HRQoL scores in the post-HSCT period were similar to those reported for conventionally treated patients. Both of these previous studies were cross-sectional and provided only limited evidence, however.

To the best of our knowledge, the present study is the first to prospectively evaluate HRQoL in thalassemia patients before and up to 18 months after HSCT. Toward this aim, we investigated 28 thalassemic children from Middle Eastern countries who underwent allogeneic HSCT from an HLA-matched donor in the bone marrow transplant centers of the IRCCS San Raffaele Hospital in Milan and the R. Binaghi Hospital in Cagliari. We also examined the level of agreement between child-self and parent-proxy ratings of HRQoL. Previous studies in childhood cancer have shown that parental ratings of their child's HRQoL tend to be lower and possibly reflect a series of parental distress factors [19,20]. In a recent review of HRQoL, the authors strongly advocate the need for prospective research into HRQoL after pediatric HSCT, with particular emphasis on the contribution of family factors [21].

METHODS

Patients and Clinical Procedures

Between November 2006 and August 2009, 28 children with thalassemia (17 males and 11 females; median age, 10 years; range, 5-17 years) underwent allogeneic HSCT from an HLA-matched donor. Patient clinical and sociodemographic characteristics are summarized in Table 1. All patients came to Italy from Middle Eastern countries to receive HSCT as part of a larger humanitarian project involving a knowledge-exchange program with the local doctors. Twenty-four patients (85.7%) were assigned to risk class 3, and the remaining 4 were assigned to risk class 2, according to the criteria proposed by Lucarelli et al. [6]. Written informed consent for HSCT was provided by the patients' parents according to the declaration of Helsinki. All patients were prepared for HSCT with a myeloablative conditioning regimen. Supportive therapy, as well as prophylaxis and treatment of infections, was homogeneous among participating centers. All patients received cyclosporine and short-term methotrexate for GVHD prophylaxis. Acute and chronic GVHD were graded according to the Seattle criteria [22,23]. After transplantation, the patients were followed up in Italy for at least 6 months, after which they returned to their home country for follow-up care. The mean duration of clinical follow-up was 24 months.

HRQoL Evaluation

HRQoL was assessed using the PedsQL 4.0 Generic Core Scales. This 23-item multidimentional questionnaire was designed to evaluate the essential core domains for pediatric HRQoL, including physical, emotional, and social functioning as defined by the World Health Organization, as well as school functioning [24,25]. The PedQL psychosocial health summary score represents the sum of items over the number of items answered in the emotional, social, and school functioning scales [26]. To create the total PedsQL score, the mean is computed as the sum of all items over the number of items answered on all scales. The reliability, internal consistency, and validity of the PedsQL questionnaire have been assessed in pediatric patients with various acute and chronic disorders, as well as in physically healthy pediatric populations [24,25]. Each item is rated on a 5-point Likert scale. The scores for each dimension are calculated as follows. The mean score is represented by the sum of the items over the number of items answered, with missing values replaced by the mean score of the remaining items. If more than 50% of the items in a given scale are missing, then the scale score is not computed. Raw scores are transformed into standardized scores on a scale of 0-100, with higher scores representing higher levels of functioning.

The PedsQL 4.0 Generic Core Scales were administered at baseline (before transplantation) and at 3 months and 6 months after HSCT while in Italy, and then at 18 months in the patients' home countries. The questionnaires were completed in Arabic.

Statistical Analysis

The survival probability of our cohort was estimated by the Kaplan-Meier method. Differences between baseline ratings and measurements performed at 3, 6, and 18 months post-HSCT were evaluated using the Mann-Whitney *U* test. Logistic regression was used to assess the association between clinical and baseline HRQoL risk factors and acute GVHD (aGVHD) onset. Risk factors considered were age (continuous), iron chelation (regular or irregular), transfusion frequency (regular or irregular), serum ferritin level >1300 μg/dL (yes or no), physical functioning, emotional functioning, social functioning, school functioning, and total score. Odds ratios (ORs) are reported with 95%

Table 1. Clinical and Sociodemographic Characteristics of 28 Children Who Underwent HSCT for Beta-Thalassemia

Characteristic	
Males/females, n	17/11
Age, years, median (range)	10 (5-17)
Language, n (%)	
Arabic	22 (79)
Sorani	6 (21)
Religion, n (%)	
Muslim	28 (100)
Country, n (%)	
Lebanon	8 (28.5)
Kurdistan (Iraq)	9 (32)
Palestine	1 (4)
Syria	10 (35.5)
Months from birth to diagnosis, median (range)	17 (1-48)
Months from birth to transfusion, median (range)	19 (2-60)
Months from birth to iron chelation therapy, median (range)	45 (12-96)
Transfusion regimen, n (%)	
Regular (pretransfusion hemoglobin ≥9 g/dL)	9 (32)
Slightly irregular (pretransfusion hemoglobin ≥7.5 and <9 g/dL)	13 (46.5)
Irregular (pretransfusion hemoglobin <7.5 g/dL or frequent transfusion reactions)	6 (21.5)
Iron chelation regimen, n (%)	
Regular administration (once daily)	5 (18)
Slightly irregular administration (at least once a week)	6 (21)
Irregular administration (less than once a week or none)	17 (61)
Hepatomegaly, n (%)	18 (64)
Hepatitis B or C infection, n (%)	12 (43)
Ferritin >1300 μg/dL, n (%)	22 (79)
Pesaro risk class, n (%)	
Class 2	4 (14.3)
Class 3	24 (85.7)
HSCT, n (%)	
Haploidentical donor	1 (3.5)
Sibling donor	25 (89.5)
Voluntary donor	2 (7)
Conditioning regimen, n (%)	
Treosulfan/thiotepa/fludarabine	6 (21)
Busulfan/cyclosporine	20 (71.5)
Busulfan/thiotepa/cyclosporine	2 (7)
aGVHD incidence, n (%)	10 (36)
aGVHD grade, n (%)	
I-II	6 (21.5)
III-IV	4 (14)
cGVHD incidence, n (%)	5 (18)
cGVHD extent, n (%)	
Limited	3 (11)
Extensive	2 (7)
Post-HSCT complications, n (%)	
Infection	19 (68)
Skin	6 (7)
Neurologic	2 (4)
Renal	4 (21)
Cardiac	1 (4)
Hepatic	1 (4)
Lung	2 (7)
Cystitis	1 (4)
Gut	3 (11)
HSCT outcome, n (%)	
Rejection	4 (14)
Mortality	3 (11)
Overall survival	25 (89)
Thalassemia-free survival	22 (79)
Follow-up, months, median (range)	24 (3-34)

confidence intervals (CI). Repeated-measures analysis of variance was used to investigate the impact of chronic GVHD (cGVHD) on the physical functioning scale and total PedsQL score. Primary analysis included the physical functioning scale; the remaining PedsQL scales (emotional and social functioning, total PedsQL score, and psychosocial health) were analyzed on an exploratory basis.

RESULTS

Clinical Outcomes

In our cohort, the Kaplan-Meier 2-year overall survival rate was 89.3%, the thalassemia-free survival rate was 78.6%, the cumulative incidence of TRM was 10.9%, and the rejection rate was 14.3%. Three patients died of a transplantation-related cause. The cumulative incidence of grade I-II and grade III-IV aGVHD was 21.5% and 14%, respectively. Five of the 25 transfusion-independent surviving patients (18%) developed cGVHD. More detailed information on outcomes is given in Table 1.

HRQoL over Time

A total of 28 children were followed up for a period of 18 months after HSCT. The response rate for QoL evaluation was 100% at baseline, 71% at 3 months post-HSCT, 64% at 6 months post-HSCT, and 68% at 18 months post-HSCT.

A primary analysis of physical functioning over time showed a decline from baseline to 3 months post-HSCT (median score, 81.3 vs 62.5; $P = .02$), followed by a sharp increase at 6 and 18 months post-HSCT, with median scores of 76.5 and 93.7, respectively. The improvement in physical functioning measured at 18 months was statistically significant compared with baseline ($P = .04$). Inspection of parent-proxy ratings revealed the same trend (Figure 1 and Table 2). Higher total PedsQL scores were observed at 18 months in children aged <10 years compared with older children, but the difference was not statistically significant.

The global ratings for well being (total PedsQL) over time were generally stable from baseline up to 3 months post-HSCT, with median scores of 81 (range, 69.4-89.7) and 75.7 (range, 69.1-82.2), respectively. These scores then rose to 80.6 (range, 66-85.6) at 6 months post-HSCT and to 94.4 (range, 79.6-96) at 18 months post-HSCT. The difference between scores at baseline and at 18 months post-HSCT was statistically significant ($P = .02$). No significant differences over time were seen for the social and emotional functioning scales or the psychosocial health summary score (Table 2).

A comparison of the level of agreement between child-self and parent-proxy ratings revealed that parents

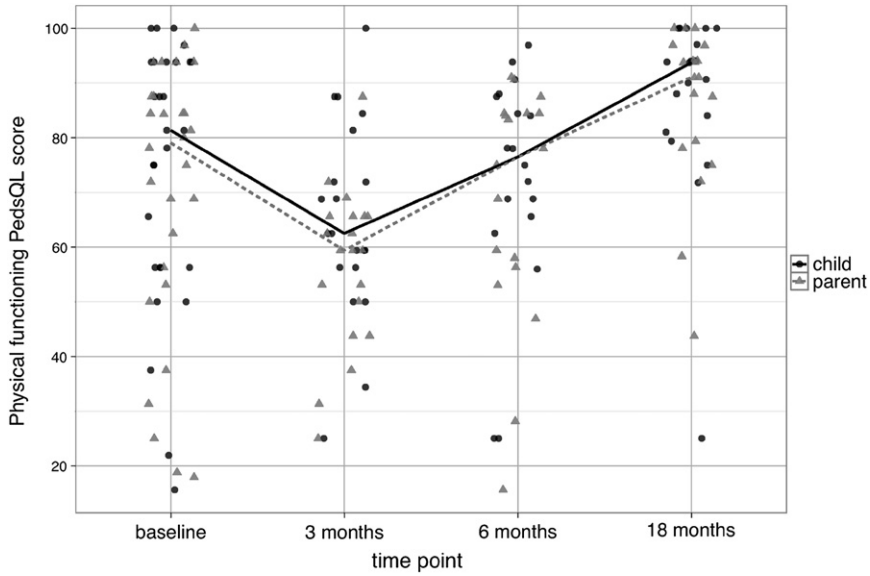

Figure 1. Physical health over time assessed by child-self and parent-proxy reports.

tended to slightly underestimate their child's QoL at all time points and in all subscales, with the sole exception of social functioning at 6 months post-HSCT. The data reported in Table 3 suggest that this underestimation of functioning levels improved over time.

GVHD and HRQoL

Univariate analysis was performed to explore possible baseline factors associated with the onset of aGVHD, including clinical risk factors and child- and parent-reported QoL, but no factor had a statistically significant relevance (data not shown). Repeated-measures analysis of variance comparing physical functioning over time between children who developed cGVHD and those who did not yielded only a marginal difference ($P = .057$). Nevertheless, a significant time effect was seen ($P < .01$), suggesting similar changes in physical functioning scores over time in the two groups of children ($P = .18$). There was a significant difference between the two groups for the total PedsQL score, with higher scores over time in the children without cGVHD ($P = .02$). A significant time effect ($P < .01$) suggested that total PedsQL scores changed differently across treatment and follow-up in these two groups ($P = .017$).

DISCUSSION

Patients with beta-thalassemia who receive conventional transfusion and iron chelation therapy complain of some of the major clinical and psychological aspects affecting HRQoL, including the impact of disease on family stability and dynamics, the difficulty of living with a chronic illness, frequent hospital visits for transfusions, and problems complying with iron chelation therapy administered as nightly s.c. infusions [12,27]. The recent introduction of oral iron-chelating drugs has improved patient compliance with treatment somewhat, but unfortunately these drugs remain unavailable in developing countries due to their high cost. Chronic disorders tend to prolong patients' dependence on family care, which significantly hampers autonomy and self-determination. Patients often need to miss work or school because of frequent medical checkups, treatments, and hospitalizations. These problems are particularly crucial in developing countries, where facilities for the control of these conditions are extremely limited. In fact, the life expectancy in developing countries is considerably lower than that of thalassemia patients born in Western countries [28]. The aim of the present study was to establish whether HSCT can actually inprove the HRQoL in children living in disadvantaged countries.

HSCT remains the sole curative treatment for beta-thalassemia. The outcome of HSCT depends in part on the patient's pretransplantation clinical condition, in particular the presence of hepatomegaly, the extent of liver fibrosis, and the magnitude of iron accumulation [6]. Thus, thalassemia patients and their families are faced with the difficult decision of whether to continue traditional therapy or accept the risks associated with the potentially curative option of HSCT. Prospective studies investigating the HRQoL of patients before and after HSCT might help solve this dilemma. Only two previous reports have studied HRQoL in thalassemia patients undergoing unrelated and sibling-matched HSCT [17,18]. Both of these studies found good HRQoL after HSCT, but the study designs were cross-sectional, and data were collected 300 days and 6.5 years after transplantation, respectively.

Our prospective study of 28 children with beta-thalassemia suggests significant improvements in

Table 2. Individual Median Scores (Range) of QoL Profiles Over Time Assessed by Child-Self and Parent-Proxy Reports

	Baseline	3 Months	6 Months	18 Months
Total PedsQL				
Child report	80.95 (69.40-89.75)	75.70 (69.08-82.25)	80.60 (66.00-85.67)	94.40 (79.60-96.00)
Parent-proxy report	72.25 (60.35-80.95)	72.80 (63.55-76.40)	74.95 (56.25-86.07)	91.30 (76.50-95.30)
Physical Functioning				
Child report	81.30 (56.30-93.80)	62.50 (56.30-74.25)	76.50 (66.40-86.72)	93.70 (82.50-98.50)
Parent-proxy report	79.05 (55.50-87.50)	59.40 (48.45-65.60)	76.50 (56.72-84.40)	91.00 (78.75-95.40)
Social Functioning				
Child report	90.00 (78.75-96.25)	88.75 (78.75-100)	87.50 (55.00-90.00)	100 (80.00-100)
Parent-proxy report	82.50 (68.75-92.50)	86.25 (73.75-96.25)	80.00 (71.25-98.75)	100 (80.00-100)
Emotional Functioning				
Child report	87.50 (73.75-90.00)	82.50 (75.00-95.00)	80.00 (71.25-87.50)	90.00 (82.50-95.00)
Parent-proxy report	70.00 (50.00-81.25)	80.00 (63.75-90.00)	70.00 (45.00-78.75)	85.00 (75.00-95.00)
Psychosocial Score				
Child report	83.30 (72.90-90.42)	82.50 (75.00-90.00)	82.75 (57.62-89.38)	93.30 (82.50-96.70)
Parent-proxy report	68.55 (60.00-80.42)	80.00 (74.38-88.12)	77.50 (58.12-89.38)	91.70 (78.00-95.80)

HRQoL after transplantation. A major outcome is that of highlighting the changes in the children's physical condition over time. The significant decline from pretransplantation levels observed at 3 months post-transplantation ($P = .02$) was followed by a significant improvement at 6 and 18 months post-HSCT ($P = .04$). The median total PedsQL score ranged from 81 at baseline to 94 at 18 months post-HSCT, suggesting significantly improved physical health. This trend was supported by the parent-proxy reports, which were in close agreement with child-reported outcomes (Figure 1). These findings are consistent with recent studies of pediatric HRQoL after HSCT for other diseases. A longitudinal measurement study of 99 pediatric patients who underwent autologous or allogeneic HSCT for leukemia, neuroblastoma, and other solid tumors showed improved physical and psychosocial HRQoL after HSCT, as reported by mothers in standardized questionnaires administered before HSCT and at 1-2 years post-HSCT [21]. In addition, a systematic review of 988 children who underwent HSCT for leukemia, myelodysplastic syndrome, lymphoma, or a solid tumor found that HRQoL was already compromised before HSCT, was further impaired immediately after conditioning, but then improved considerably by 4-12 months post-HSCT [29].

The poor HRQoL that we observed in the early post-HSCT phase can be attributed to the toxicity burden of chemotherapy reported by patients during and immediately after HSCT, as well as the number of stressful events (eg, isolation in a protected environment for 1-2 months, social isolation following hospital dismissal, increased dependency on parents, difficulty resuming age-appropriate activities). Indeed, at the 3-month post-HSCT assessment, our results for overall child well-being (as measured by the total PedsQL scale), did not show significant differences. However, at 6 months post-HSCT, we found a steady improvement on this scale, which reached statistical significance at 18 months post-HSCT ($P = .02$) (Table 2). We also noted improved psychosocial, social, and emotional functioning (Table 2).

The secondary aim of the present study was to compare parents' and children's perspectives of HRQoL before and after transplantation. Figure 1 and Table 2 show considerable overlap between child and parent perceptions of HRQoL. However, comparing the level of agreement between child-self and parent-proxy ratings revealed a slight tendency of the parents to underestimate their child's HRQoL on all subscales at all time points. Interestingly, this parental underestimation of child functioning improved over time (Table 3). The initial differences in perception most likely can be attributed to worries or distress factors surrounding the early post-HSCT period, when the child's clinical condition is generally worse [19,20].

Chronic GVHD had a major impact on both physical functioning and overall well being. The children who developed cGVHD did not recover to the same

Table 3. Mean Differences between Patient and Parent Scores on the PedsQL 4.0 at Different Time Points

	Baseline	3 Months	6 Months	18 Months
Physical functioning	4.2 (20)	8.3 (16.5)	4.0 (8.4)	1.3 (8.8)
Emotional functioning	13.4 (19.2)	6.5 (22.9)	8.9 (10.9)	3.2 (13.3)
Social functioning	6.6 (25.4)	0.5 (18.9)	−0.6 (21.5)	2.2 (7.3)
School functioning	1.2 (21.5)	NA	NA	NA
Total PedsQL score	6.5 (15.6)	5.6 (11.9)	4.5 (7.4)	2.0 (6.3)

NA indicates not assessed.

Positive signs imply underestimation by the parents, whereas negative signs imply overestimation. School functioning over time was not assessed, because the children did not attend regular lessons during the study period.

extent as those who did not develop cGVHD, even at 18 months post-HSCT. This finding underscores the importance of taking every available step to reduce this serious complication. No significant correlations were found among clinical baseline risk factors, HRQoL scores at baseline, and development of aGVHD. Our cohort was relatively small and included only children who received a transplant from a matched sibling donor, however. Our research team is currently collecting data on the HRQoL of thalassemia patients receiving transplants from unrelated donors. Although larger studies are warranted, our findings suggest improved HRQoL in thalassemia patients after HSCT and definitely add to the scanty literature on this topic. The important evidence-based data emerging from the PedsQL questionnaire should help clinicians and patients alike to make more informed treatment decisions. Child-self and parent-proxy reports represent a valid methodological approach and make it possible to obtain unique information on the HRQoL of pediatric patients. Overall, our study provides further insight into the difficult clinical decision making process that surrounds the choice of HSCT for chronic nonmalignant diseases [30-32].

ACKNOWLEDGMENTS

We thank all of our little patients and their parents for participating in this study and taking the time to complete the questionnaires. We also thank Dr. James Varni and the Mapi Research Institute for the use of the Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales, and Anna Maria Koopmans for her assistance in preparing the manuscript.

Financial disclosure: The authors have no conflicts of interest to disclose.

REFERENCES

1. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*. 2004;89:1187-1193.
2. Borgna-Pignatti C. Surviving with thalassemia major: the Italian experience. *Pediatr Hematol Oncol*. 2007;24:75-78.
3. Rund D, Rachmilewitz E. β-Thalassemia. *N Engl J Med*. 2005; 353:1135-1146.
4. Atkin K, Ahmad W. Living a "normal life": young people coping with thalassemia major or sickle cell disorder. *Soc Sci Med*. 2001; 53:615-626.
5. Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. *N Engl J Med*. 1990;322: 417-421.
6. Lucarelli G, Giardini C, Angelucci E. Bone marrow transplantation in thalassemia. *Cancer Treat Res*. 1997;77:305-315.
7. Lucarelli G, Gaziev J. Advances in the allogeneic transplantation for thalassemia. *Blood Rev*. 2008;22:53-63.
8. La Nasa G, Giardini C, Argiolu F, et al. Unrelated donor bone marrow transplantation for thalassemia: the effect of extended haplotypes. *Blood*. 2002;99:4350-4356.
9. Schumacher M, Olschewski M, Schulgen G. Assessment of quality of life in clinical trials. *Stat Med*. 1991;10:1915-1930.
10. Leplege A, Hunt S. The problem of quality of life in medicine. *JAMA*. 1997;278:47-50.
11. Efficace F, Sprangers M. Designing and interpreting quality-of-life and other patient-reported outcomes in clinical trials. In: *Education Program for the 14th Congress of the European Hematology Association (EHA Educational Book 14)*. Berlin, Germany: European Hematology Association; 2009. p. 89-95.
12. Tefler P, Constantinidou G, Andreou P, et al. Quality of life in thalassemia. *Ann N Y Acad Sci*. 2005;1054:273-282.
13. Pakbaz Z, Treadwell M, Yamashita R, et al. Quality of life in patients with thalassemia intermedia compared to thalassemia major. *Ann N Y Acad Sci*. 2005;1054:457-461.
14. Dahlui M, Hishamshah MI, Rahman AJ, et al. Quality of life in transfusion-dependent thalassemia patients on desferrioxamine treatment. *Singapore Med J*. 2009;50:794-799.
15. Scalone L, Mantovani LG, Krol M. Costs, quality of life, treatment satisfaction and compliance in patients with beta-thalassemia major undergoing iron chelation therapy: the ITHACA study. *Curr Med Res Opin*. 2008;24:1905-1917.
16. Ismail A, Campbell MJ, Ibrahim HM, et al. Health-related quality of life in Malaysian children with thalassemia. *Health Qual Life Outcomes*. 2006;4:39-46.
17. Caocci G, Pisu S, Argiolu F, et al. Decision-making in adult thalassemia patients undergoing unrelated bone marrow transplantation: quality of life, communication and ethical issues. *Bone Marrow Transplant*. 2006;37:165-169.
18. Cheuk DK, Mok AS, Lee AC, et al. Quality of life in patients with transfusion-dependent thalassemia after hematopoietic SCT. *Bone Marrow Transplant*. 2008;42:319-327.
19. Speechley KN, Barrera M, Shaw AK, et al. Health-related quality of life among child and adolescent survivors of childhood cancer. *J Clin Oncol*. 2006;24:2536-2543.
20. Forinder U, Lof C, Winiarski J. Quality of life following allogeneic stem cell transplantation, comparing parents' and children's perspective. *Pediatr Transplant*. 2006;10:491-496.
21. Barrera M, Atenafu E, Hancock K. Longitudinal health-related quality of life outcomes and related factors after pediatric SCT. *Bone Marrow Transplant*. 2009;44:249-256.
22. Thomas ED, Storb R, Clift RA, et al. Bone marrow transplant. *N Engl J Med*. 1975;292:832-843.
23. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man: a long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69:204-217.
24. Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory generic core scales, mutidimensional fatigue scale, and cancer module. *Cancer*. 2002;94:2090-2106.
25. Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population measure: feasibility, reliability, and validity. *Qual Life Res*. 2006;15:203-215.
26. Varni JW. The PedsQL measurement model for the Pediatric Quality of Life Inventory. Available from: http://www.pedsql.org/about_pedsql.html. Accessed July 6, 2010.
27. World Health Organization. Measuring quality of life. Available from: http://www.who.int/evidence/assessement-instrument/QOL/index.ht/. Accessed July 6, 2010.
28. Borgna-Pignatti C. The life of patients with thalassemia major. *Haematologica*. 2010;3:345-348.
29. Clarke SA, Eiser C, Skinner R. Health-related quality of life in survivors of BMT for pediatric malignancy: a systematic review of the literature. *Bone Marrow Transplant*. 2008;42:73-82.
30. Lucarelli G, Weatherall DJ. For debate: bone marrow transplantation for severe thalassaemia. *Br J Haematol*. 1991;78: 300-303.
31. Weatherall DJ. The treatment of thalassemia: slow progress and new dilemmas. *N Engl J Med*. 1993;329:877-879.
32. Giardini C. Ethical issue of bone marrow transplantation for thalassemia (editorial). *Bone Marrow Transplant*. 1995;15:657-658.