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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%