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Allogeneic Hematopoietic Cell Transplantation for Children with Sickle Cell Disease Is Beneficial and Cost-Effective: A Single-Center Analysis

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Limited data exist regarding health care utilization (HCU) in patients receiving allogeneic hematopoietic cell transplantation (alloHCT) for sickle cell disease. Financial data from 2002 to 2011 were analyzed for 26 alloHCT patients and 48 control subjects (referred but without alloHCT). HCU of alloHCT was determined over 3 time periods: pre-alloHCT, during alloHCT (day 0 to day +365), and post-alloHCT. The median total cost per patient during the alloHCT year was $413,000 inpatient and $18,000 outpatient. Post-alloHCT HCU decreased when compared with pre-alloHCT and control subjects. The median cost of post-alloHCT outpatient visits per patient was significantly less when compared with pre-alloHCT ($P = .044$). The median cost of post-alloHCT inpatient visits per patient approached significance when compared with those pre-alloHCT ($P = .079$). Sixteen post-alloHCT patients, 19 control subjects, and 14 unaffected siblings were surveyed using Pediatric Quality of Life Inventory and EuroQOL questionnaires; however, the questionnaire scores across all 3 patient groups were not statistically significant ($P = .2638$). When adjusted for health-related quality of life, the analysis suggested alloHCT has a positive impact on health-related quality of life over control subjects. These pilot data support our hypothesis that alloHCT in children with sickle cell disease reduces HCU compared with control subjects without alloHCT.

INTRODUCTION

Patients with sickle cell disease (SCD) are plagued with substantial morbidity, decreased life expectancy, and high health care utilization (HCU). The treatment and management of SCD is a substantial public health need. Currently, allogeneic hematopoietic cell transplantation (alloHCT) is the only curative option for patients with SCD and has seen dramatic improvements in outcomes over the past 2 decades. As a result, alloHCT has become more available and more readily recommended for even younger patients and/or those with less severe disease. Therefore, the impact of this shift in management must be analyzed in a way that addresses outcomes, HCU, and health-related quality of life (HRQOL). This analysis is integral for patient decision-making and has substantial public policy implications.

SCD affects approximately 100,000 people in the United States, and each year 2000 new diagnoses are detected via newborn screening [1]. Over their lifetime, children with SCD suffer from disease-related complications that have an adverse impact on quality of life and can lead to premature death. These complications directly translate into substantial HCU among this population.

Many studies have examined the clinical outcomes and health care costs of SCD. In a study by Mvundura et al. [2], US children with SCD represented > 1500 visits to the emergency room and >1200 hospitalizations per year. In a subsequent 2010 study, the total pediatric SCD-attributable expenditures in the United States were estimated to be about $335 million per year [3]. The US population of individuals with SCD reflects substantial HCU of up to $1.6 billion per year [4]. In the posthydroxyurea era, life expectancy for sickle cell patients has increased from 30 years to greater than 40 years, but this remains only about half that of individuals without SCD in the United States [5]. With the increase in life expectancy, the total annual hospitalization

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cost has been documented at over $15 million for adults and $2 million for children treated in the state of Maryland [6]. This difference in annual costs is attributed to the persistence of SCD-related complications and irreversible end-organ damage in adults even after the implementation of hydroxyurea therapy. These figures not only represent the financial impact on our health care system but also the continued medical needs not being met by our current treatment strategies.

Ultimately, these data must be adequately compared with health outcomes and the cost of receiving alloHCT for SCD. A number of studies have investigated curative approaches, including alloHCT [7,8]. The success rate has risen to a 5-year disease-free survival of 85% and an overall survival of 97% with associated lower rates of post-alloHCT morbidity [9]. These outcomes improve further when limited to matched sibling donor (MSD) alloHCT, thus making alloHCT a far more viable option [10].

However, alloHCT carries a significant financial cost in the first year but then subsequently decreases rapidly over time. The reported cost of alloHCT for adults with malignant or nonmalignant conditions in the first year ranges from $96,000 to $204,000 [11]. This cost can vary based on conditioning regimen, allograft type, and donor source. However, limited data exist on the cost associated with receiving alloHCT for children with SCD.

Data on the impact of alloHCT on HRQOL are also limited. It has been shown among pediatric alloHCT recipients that HRQOL is worst immediately post-alloHCT but improves substantially over time [12]. Kelly et al. [13] investigated this among pediatric alloHCT recipients for hemoglobinopathies and found a similar reduction in HRQOL immediately post-alloHCT with return to baseline at 3 months post-alloHCT. To date, no studies evaluate HRQOL in an isolated population of children with SCD beyond 1 year post alloHCT and correlate this with health care costs. In this pilot study, we hypothesize that alloHCT will reduce HCU and cost when compared with SCD control subjects while improving HRQOL.

METHODS

Patients and Eligibility

Patients aged 21 years or less were from the New York Presbyterian Morgan Stanley Children's Hospital of Columbia University Medical Center with homozygous hemoglobin S disease, sickle hemoglobin C disease, sickle β^+-thalassemia, or sickle β^0-thalassemia. Control subjects were children with SCD with documented HLA typing and/or alloHCT consultation during the study period. Cases included eligible recipients of alloHCT within the study period.

Patients received either a myeloablative conditioning regimen, which consisted of busulfan (16 mg/kg), cyclophosphamide (120 to 200 mg/kg) ± rabbit antithymocyte globulin (8 mg/kg) or busulfan (12.8 to 16 mg/kg), fludarabine (180 mg/m^2), and alemtuzumab (54 mg/m^2), or a reduced-intensity conditioning regimen, which consisted of melphalan (140 mg/m^2), fludarabine (180 mg/m^2), and alemtuzumab (54 mg/m^2). When used, alemtuzumab was administered proximally. Acute graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus ± mycophenolate mofetil. In addition, hospital standard operating practice was used for seizure prophylaxis as well as infection prevention and prophylaxis as published previously [10].

Interrogating the Database

A retrospective review of the internal financial data collected was performed. This database contained cost and HCU information for each patient encounter within the hospital, emergency department, or ambulatory setting and served as the pilot cohort of data. Of note, the database did not include any data on physician fees or cost. To date, our database includes over 200 patients with SCD, and an additional 26 patients received alloHCT for SCD from 2002 to 2012.

Study patients were identified using unique diagnostic codes. The database was first searched to identify disease-specific alloHCT patients using ICD-9 code 282.6 (*International Classification of Diseases, Ninth Revision*) and alloHCT codes and/or descriptions. The generated patient list was then compared with internal bone marrow transplant database records to ensure data capture and accuracy. Once validated, a complete database search was performed to obtain HCU information using patient medical record numbers from the internal bone marrow transplant database for alloHCT patients and alloHCT referrals.

Costs were recorded in terms of direct, indirect, and total costs from the perspective of the health care institution or hospital; total costs were used as the cost variable for analysis. Data on charges were also provided; however, cost data only were analyzed as charges vary. These cost data included patient care setting (outpatient, inpatient, etc.) as well as inpatient length of stay (LOS), number of inpatient visits, and number of outpatient visits.

Determining Costs and Utilization

The above financial data were analyzed across the 2 groups: the alloHCT case group and the control group. The HCU for the alloHCT group was determined over 3 time periods: pre-alloHCT (before the start of conditioning), during the alloHCT year (start of the conditioning regimen to day +365), and post-alloHCT (beyond day +365). Control patients were analyzed over the duration of care at the institution within the study period of 2002 to 2012.

To provide statistically relevant analysis, patients with less than 6 months of financial data within the pre- or post-alloHCT periods of the study were excluded. This included 5 patients who transferred care to another institution with their primary transplant attending and therefore lacked complete post-alloHCT data. Another 3 patients were referred to our institution for alloHCT and therefore lacked sufficient pre-alloHCT data. An additional 4 patients died during the alloHCT year and therefore lacked post-alloHCT data. Because of the small sample size, HCU data could not be extrapolated for inclusion in the analysis, making these patients unassessable in the comparative analysis. This resulted in an assessable sample size of 14 patients for HCU. However, all alloHCT patients had assessable data during the alloHCT year and were therefore included in the analysis for this period. The data from this time period of the study were not used for case-control comparative analysis.

Because the amount of data available for alloHCT patients varied based on date of transplant within the study period, all HCU variables were determined in terms of HCU per patient per month. This established a standard or constant data point for comparison between patients and patient groups.

HRQOL

Surviving alloHCT recipients and control subjects were surveyed after HCU data collection using age-appropriate Pediatric Quality of Life Inventory (PedsQL) and EuroQOL (EQ-5D) questionnaires. Post-alloHCT siblings without SCD were also surveyed as the unaffected control subjects. PedsQL queries HRQOL across 4 scales—physical, emotional, social, and school functioning—based on recall over the past month [14]. A total scaled score was then determined using the PedsQL scoring algorithm.

EQ-5D provides a 2-part assessment of 5 dimensions of functioning—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—as experienced at the time of the survey and an overall self-report of health status in the visual analogue scale (VAS) [15]. Mean HRQOL scores (maximum score of 100 for PedsQL and EQ-5D VAS) were calculated for each of the 3 groups. Utility scores were determined based on EQ-5D responses using established valuation methods and US value sets [16]. Scores were compared using Wilcoxon rank sum ordering to determine significance.

The quality-adjusted life year (QALY) for each patient in the alloHCT year was then determined using the sum of the interval average utilities and time at days +45, +90, +180, and +365 based on utility norms from previously published data [13]. To compare alloHCT patients to control subjects, the incremental cost-effectiveness ratio (ICER), the ratio of the change in costs to incremental benefits of alloHCT, was calculated as the difference in annual costs for the comparison groups divided by the change in QALY as determined using the area under the curve [17].

Statistical Considerations

Most of the HCU analysis was descriptive. The cumulative HCU per patient depended on the follow-up time and can be influenced by terminal event death. Those patients without corresponding inpatient HCU variables to outpatient were assigned 0 value for calculations. The mean and standard deviation (SD) were calculated; median and range were also reported.

The comparison between pre- and post-alloHCT groups was carried out using the generalized linear models with identity link and normal error for the comparison of the cost of inpatients and cost of outpatients and by the generalized linear models with Poisson distribution and log link for the