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Relationship of Body Mass Index and Arm Anthropometry to Outcomes after Pediatric Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies

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A B S T R A C T

Although nutritional status may adversely affect various health outcomes, the relationship between anthropometry and outcomes after hematopoietic cell transplantation (HCT) has not been fully studied in children. We analyzed the impact of pre-HCT body mass index (BMI), arm muscle area, and arm fat area on outcomes in 733 patients age 2-18 years who underwent allogeneic HCT for a hematologic malignancy between 1985 and 2009. We evaluated these 3 variables according to patient group based on age- and sex-adjusted percentiles for BMI, arm muscle area (<5th, 5th-24th, 25th-94th, and ≥95th), and arm fat area (<25th, 25th-94th, and ≥95th). Cox proportional hazards regression models for event-free survival (EFS), relapse, and nonrelapse mortality (NRM) at 100 days and 3 years after HCT, as well as grade II-IV acute graft-versus-host disease (GVHD) and chronic GVHD, were performed using the 3 major variables and adjusted for covariates. BMI was <5th percentile in only 3% of patients and ≥95th percentile in 15% of patients, but outcomes for both groups were similar to those for the BMI 25th-94th percentile group. The BMI 5th-24th percentile group had lower EFS ($P = .01$) and higher relapse ($P = .003$) at day +100 post-HCT, but these associations did not hold at 3 years post-HCT. Arm muscle area was <5th percentile in 8% of patients, and arm fat area was <25th percentile in 10%. Analysis of arm muscle area showed that the <5th percentile group had lower EFS and higher NRM and relapse rate at day +100 ($P = .002$, .04, and .01, respectively) and 3 years ($P = .0004$, .008, and .01, respectively) post-HCT. Arm fat area <25th percentile was associated with lower EFS at day +100 (hazard ratio, 1.5; $P = .05$), but not at 3 years post-HCT. Anthropometry variables were not associated with acute or chronic GVHD. In conclusion, arm muscle area <5th percentile appears to be a stronger predictor than BMI of poor outcomes after HCT in children with hematologic malignancies.

INTRODUCTION

Poor nutritional status is known to adversely affect health outcomes. The role of nutritional status in children undergoing hematopoietic cell transplantation (HCT) is not fully understood. Early studies of pediatric HCT using ideal body weight showed poor survival in underweight patients after transplantation, but no difference in survival in overweight patients [1,2]. Since then, body mass index (BMI) has become a more commonly used index of nutritional status. In 2 studies, overweight patients (BMI ≥95th percentile) demonstrated decreased survival compared with non-overweight children [3,4].

BMI might not be the best indicator of nutritional status or body composition in pediatric HCT patients given that BMI only indicates weight relative to height (body size), and cannot discriminate between fat and muscle mass [5]. But body composition can be estimated by arm anthropometry, which measures peripheral tissue and provides an approximation of whole-body muscle and fat mass. Although arm anthropometry is not widely done, it is routinely performed at our center.

The purpose of the present study was to determine whether BMI and body composition as measured by arm anthropometry are associated with survival outcomes and the development of acute and chronic graft-versus-host disease (GVHD) in a large population of pediatric patients undergoing HCT for hematologic malignancies.

PATIENTS AND METHODS

Patient Selection

Between 1985 and July 1, 2009, 822 consecutive children age 2-18 years underwent myeloablative conditioning and allogeneic HCT for a hematologic malignancy at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle. Thirty-two of these patients were excluded from the present analysis, including 9 who received a T cell–depleted allograft, 6 who did not consent to follow-up, 5 who received ^{131}iodine therapy, 5 with Down syndrome, 4 who received 10-Gy single-fraction total body irradiation (TBI), and 3 identical twin donor allograft recipients. The remaining 790 patients or their responsible guardians consented to follow-up under Protocol 999.2, and the data were reviewed under Protocol 1782 approved by the FHCRC Institutional Review Board.

Anthropometric data were unavailable for 57 patients (23 for undocumented reasons, 20 for patient refusal or uncooperativeness, 9 not tested owing to direct hospital admissions, 4 for obesity, and 1 with missing data), leaving a total of 733 patients for analysis. Compared with the patients with anthropometric data, the 57 patients without anthropometric data were younger (7.5 years versus 10.4 years; $P < .001$) at time of transplantation, but there were no statistical differences in transplantation outcomes (data not shown).

Preparative Regimens, Stem Cell Sources, and Supportive Care

Transplantation preparative regimens included either chemotherapy or chemoradiotherapy as described previously [6-10]. Most chemotherapy-only

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regimens used cyclophosphamide 50 mg/kg/day for 4 days combined with busulfan 4 mg/kg/day for 4 days [6,8]. Most of the busulfan and cyclophosphamide doses were calculated using adjusted body weight if the patient's actual weight was >100% of ideal body weight, when dosing was based on per-kilogram weight. Since 1992, most busulfan doses have been adjusted based on pharmacokinetic levels [11]. Most TBI regimens included cyclophosphamide 60 mg/kg/day for 2 days. Between 1985 and 2000, TBI was delivered from dual opposing cobalt-60 sources at a dose rate in air of 5-8 cGy/min as fractionated TBI, with exposures of 2.0-2.75 Gy for 6-7 consecutive days or hyperfractionated exposures of 1.2 Gy 2-3 times daily for 4 consecutive days [6,9,10]. Starting in 2001, TBI has been delivered by a linear accelerator.

The allogeneic transplantation recipients received bone marrow, peripheral blood, or umbilical cord blood stem cells harvested from related or unrelated donors. All allogeneic transplantation recipients received prophylaxis for acute GVHD depending on the type of donor and protocol in use at the time of HCT and generally including either methotrexate or methotrexate and a calcineurin inhibitor, but less often including corticosteroids, antithymocyte globulin, mycophenolate mofetil, or monoclonal antibodies as additional prophylactic agents [12-14]. Acute and chronic GVHD were diagnosed, graded, and treated as described previously [15-18].

All surviving patients underwent evaluation for engraftment and chronic GVHD at 80-100 days after transplantation. Patients returned to the FHCRC for long-term follow-up at 1 year and electively thereafter. Follow-up after 1 year consisted of annual contact with referring physicians between 1985 and 1990, and questionnaires mailed annually to patients and their primary medical providers from 1991 to present.

Study Data

Data were obtained from the FHCRC clinical information database, transplantation flowsheets, nutritional records, and long-term follow-up records. Study data were collected through July 1, 2012.

BMI (in kg/m^2) was calculated based on patient height and weight at the time of HCT. Sex- and age-adjusted BMI was calculated using the 2000 Centers for Disease Control and Prevention's BMI for age growth charts to obtain percentile rankings [19]. Patients were divided into 4 BMI categories: underweight (<5th percentile), at risk for underweight (5th to <25th percentile), normal and at risk for overweight (25th to <95th percentile), and overweight (≥95th percentile).

Arm anthropometry was performed by registered dietitians. Mid-upper arm circumference was measured with flexible tape to the nearest 0.1 cm, and triceps skin fold thickness was measured with a Harpenden skinfold caliper as the average of 3 measurements taken to the nearest 0.2 mm at the halfway point between the acromion and olecranon process of the right upper arm. Arm muscle area and arm fat area *z*-scores were calculated according to the equations and age and sex-matched norms of Frisancho [20] and expressed as percentiles. Patients were divided into 4 arm muscle area categories: <5th percentile, 5th to <25th percentile, 25th to <95th percentile, and ≥95th percentile. Because of a limited number of patients in the <5% percentile category, arm fat area was collapsed into 3 categories: <25th percentile, 25th to <95th percentile, and ≥95th percentile.

Study Endpoints, Variables, and Statistical Methods

For the purpose of analysis, patient diagnoses at HCT were categorized into 4 groups: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and juvenile myelomonocytic leukemia and myelodysplastic syndrome. Variables selected for adjustment included sex, race/ethnicity (non-Hispanic white versus other race/ethnicity), diagnosis, time from diagnosis to HCT (<1 year versus ≥1 year), age at HCT (2-9 years versus 10-18 years), TBI (yes/no), donor type (related versus unrelated), donor–recipient HLA-matching (matched or mismatched, defined as at least 1 antigen mismatch at HLA-A, -B, or -DRB1), acute GVHD prophylaxis (use of 1, 2, or 3 or more prophylactic drugs), and disease status. For the latter, good risk included ALL and AML in first or second complete remission (CR), CML in chronic phase, juvenile myelomonocytic leukemia and myelodysplastic syndrome, and myelodysplastic syndrome in refractory anemia or refractory anemia with ringed sideroblasts, and poor risk included ALL and AML in active relapse or third or greater CR, CML in acute phase or blast crisis, and myelodysplastic syndrome in refractory anemia with excess blasts or excess blasts in transformation.

Primary endpoints were nonrelapse mortality (NRM), relapse, and event-free survival (EFS) over the first 100 days and the first 3 years posttransplantation, and the development of grade II-IV acute GVHD and clinical extensive chronic GVHD. NRM was defined as death in CR. Relapse was defined as recurrence of disease in bone marrow. EFS was defined as survival without death, relapse, graft failure, or secondary malignancy.

All endpoints were adjusted for diagnosis, sex, race/ethnicity, age at HCT, TBI, donor type, and HLA matching. NRM, EFS, and relapse were also adjusted for disease status and time from diagnosis to HCT. Acute GVHD was also adjusted for acute GVHD prophylaxis.

Survival curves were estimated by the Kaplan-Meier method. Cox regression was used for hazard ratio (HR) analysis, with adjustment for covariates. NRM and relapse were treated as mutually competing risks. Death was treated as a competing risk for analysis of acute and chronic GVHD. Overall tests of significance reflect likelihood ratio tests; comparisons of individual levels to the reference level reflect Wald tests. All *P* values are 2-sided. Descriptive data were analyzed using SPSS software (IBM, Armonk, NY). Descriptive statistics are reported as mean and range.

RESULTS

Patient Population

Patient and transplantation characteristics are presented in Table 1. The study population comprised 733 patients, of whom 60% were male, 54% had ALL and 26% had AML, 56% were good risk, and 65% had received a HLA-matched transplantation from a sibling (41%), unrelated (37%), or other related (22%) donor. The distribution of patient BMI and arm anthropometry is shown in Table 2. Three percent of the patients were underweight (BMI <5th percentile), and 15% were overweight (BMI ≥95th percentile). Arm muscle area was very low (<5th percentile) in 8%, and arm fat area was low (<25th percentile) in 10%. Pearson correlation coefficients for the 3 measures were as follows: BMI with arm muscle area, $r = 0.60$, $P < .0001$; BMI with arm fat area,

Table 1
Patient and Transplantation Characteristics

Characteristic	Value
Number of patients	733
Age at HCT, yr, median (range)	9.2 (2.0-17.9)
Sex, n (%)	
Female	297 (40)
Male	436 (60)
Race/ethnicity, n (%)	
Non-Hispanic white	574 (78)
Other race/ethnicity	159 (22)
Diagnosis at HCT, n (%)	
ALL	395 (54)
AML	189 (26)
CML	89 (12)
Juvenile myelomonocytic leukemia	15 (2)
Myelodysplastic syndrome	45 (6)
Disease phase, n (%)	
Good	410 (56)
Poor	323 (44)
Donor type for first HCT, n (%)	
Related (parent or relative)	159 (22)
Unrelated	269 (37)
Sibling	305 (41)
HLA matching, n (%)	
Matched	475 (65)
Mismatched	258 (35)
Stem cell source at first HCT, n (%)	
Bone marrow	645 (88)
Peripheral blood	50 (7)
Cord blood	38 (5)
HCT preparative regimen, n (%)	
Fractionated 12-15.75 Gy TBI	637 (87)
Non–TBI-containing regimens	
Busulfan + cyclophosphamide	86 (12)
Other	10 (1)
Acute GVHD prophylaxis agents, n (%)	
1	103 (14)
2	562 (77)
3+	68 (9)
Acute GVHD grade, n (%)*	
0-I	190 (26)
II-IV	541 (74)
Clinical extensive chronic GVHD (yes/evaluable), n (%)	241/526 (46)

* Two patients were not evaluable for acute GVHD.