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Cardiovascular Risk Factors in Survivors of Childhood Hematopoietic Cell Transplantation Treated with Total Body Irradiation: A Longitudinal Analysis

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Hematopoietic cell transplantation (HCT) survivors treated with total body irradiation (TBI) are known to be at increased risk for the development of cardiovascular risk factors (CVRFs). We sought to characterize the incidence of CVRFs in a TBI-exposed survivor cohort and to describe prognostic indicators of their development through a retrospective analysis of CVRFs in 1-year survivors of leukemia or lymphoma treated with TBI at Memorial Sloan Kettering between April 1987 and May 2011. Eligible participants were age ≤21 years at the time of TBI and were not receiving glucocorticoid therapy at the time of entry to long-term follow-up. Survivors were assessed for obesity (body mass index ≥95th percentile for age ≤ 20 years and ≥30 kg/m^2 for age >20 years), elevated blood pressure, dyslipidemia (elevated triglycerides [TG], low high-density lipoprotein [HDL]), and glucose intolerance (fasting glucose ≥100 mg/dL); those with ≥3 risk factors were deemed to have a CVRF cluster, a surrogate for metabolic syndrome. Cox regression models were used to estimate hazard ratios (HRs) for factors associated with each CVRF. To compare the prevalence of CVRFs in HCT survivors and the general population, survivors were compared with age-, sex-, and race-matched controls from the National Health and Nutrition Examination Survey. A total of 123 survivors were evaluated (62.6% males). The median age at TBI was 11.8 years (range, 1.6 to 21.9 years). The median duration of follow-up was 8.0 years (range, 1.01 to 24.6 years), and the median age at last follow-up was 20.1 years (range, 4.0 to 41.3 years). The 5-year cumulative incidence was 14.7% for elevated blood pressure, 10.5% for elevated glucose, 26.8% for low HDL, 39.2% for hypertriglyceridemia, and 16.0% for obesity, and corresponding 10-year cumulative incidences of 28.8%, 33.1%, 52.0%, 65.0%, and 18.6%. The median cumulative incidence of a CVRF cluster rose from 10.6% (range, 5.6% to 17.5%) at 5 years to 28.4% (range, 18.8% to 38.7%) at 10 years. In multivariate analysis, growth hormone (GH) deficiency (hazard ratio [HR], 8.6; 95% confidence interval [CI], 2.1 to 34.4; $P = .002$), history of cranial radiation (HR, 4.0; 95% CI, 1.7 to 9.6; $P = .002$), and grade II-IV acute graft-versus-host disease GVHD (HR, 4.2; 95% CI, 1.5 to 12.2; $P = .008$) were associated with the risk of developing a CVRF cluster. Compared with a random sample of matched population controls, HCT survivors had an increased prevalence of hypertriglyceridemia and low HDL, but not of glucose intolerance, elevated blood pressure, or CVRF cluster. Given the young age of this HCT survivor cohort, these data highlight the importance of routine screening for CVRF starting in childhood in individuals exposed to TBI.

INTRODUCTION

Advances in hematopoietic cell transplantation (HCT) and supportive care have resulted in improved survival rates for patients with high-risk hematologic malignancies [1-3]. Nonetheless, long-term survivors remain at increased risk for treatment-related morbidity [4-6], including multiple cardiovascular risk factors (CVRFs), such as obesity, elevated blood pressure, glucose intolerance, and dyslipidemia [7-10]. Taken together, these factors constitute the so-called metabolic syndrome, a constellation of abnormalities associated with increased all-cause and cardiovascular mortality [11,12].

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Previous studies have demonstrated an increased prevalence of metabolic syndrome and its components in HCT survivors [8,9,13-22]. Exposure to total body irradiation (TBI) has been identified as an independent risk factor for the development of CVRFs [8,14,23-25]. In a large single-institution study of 1885 1-year HCT survivors (median age at HCT, 44.4 years; 30.5% treated before age 35; 52.7% treated with TBI), the prevalence of CVRFs was significantly higher among HCT survivors compared with the general population. Moreover, compared with HCT survivors not exposed to TBI-based conditioning regimens, those treated with TBI were at 1.5-fold increased risk for the development of diabetes mellitus and 1.4-fold increased risk for dyslipidemia [8]. Others have similarly demonstrated an increased risk of metabolic derangements in individuals exposed to TBI [13,14,17,18, 23,26].

Nonetheless, data are lacking on longitudinal changes in CVRFs and the contribution of demographic and other therapeutic exposures to the risk in individuals exposed to TBI during childhood. In the present study, we sought to fill this gap using a single-institutional cohort of long-term HCT survivors treated with TBI during childhood to (1) determine the longitudinal changes in CVRFs as this survivor population ages, (2) identify demographic and treatment factors associated with the development of metabolic derangements in this population, and (3) compare the prevalence of CVRFs with that in age-, race-, and sex-matched population controls.

METHODS

We performed a retrospective analysis of CVRF in 1-year HCT survivors treated with TBI at Memorial Sloan Kettering (MSK) between April 1987 and May 2011. All data were obtained from review of the MSK medical record, which includes internal documentation as well as outside correspondence with survivors' local physicians. The protocol was approved by the MSK Institutional Review Board/Privacy Board.

Subjects

Eligible participants had a primary diagnosis of leukemia or lymphoma, were age ≤21 years at the time of TBI, and had survived at least 1 year relapse-free from the date of HCT. All participants had been seen at least once in one of the long-term follow-up (LTFU) clinics at MSK, which provide risk-based comprehensive follow-up care to individuals who have survived at least 1 year after the completion of cancer-directed therapy. All patients underwent serial assessments of height, weight, blood pressure, fasting glucose, and fasting lipid panel, as would be recommended by the Children's Oncology Group LTFU guidelines [27].

Patients were censored at the date of relapse. Any survivor who underwent HCT more than once was excluded. In addition, in an effort to exclude those with active graft-versus-host disease (GVHD) and avoid potential confounding associated with glucocorticoid use, individuals receiving glucocorticoid therapy at the time of their first LTFU visit for at least 3 months were excluded as well (n = 11). Indications for glucocorticoid use among excluded individuals were chronic GVHD (n = 7), post-transplantation autoimmune hemolytic anemia (n = 1), nonspecific arthritis (n = 1), rejection prophylaxis after renal transplantation for post-HCT renal failure (n = 1), and recurrent bronchiolitis obliterans organizing pneumonia (n = 1).

Exposure Data

Demographic information was abstracted from the medical record (Table 1). Race/ethnicity was self-reported by the patient and/or family. Post-treatment complications, including thyroid dysfunction, sex hormone deficiency, and documented growth hormone (GH) deficiency, as well as dates of treatment when relevant, were recorded.

Treatment exposures included pre-HCT chemotherapy, high-dose chemotherapy related to the conditioning regimen, and sites and doses of radiation therapy were abstracted from the medical record. Details related to transplantation-related exposures, including donor type, stem cell source, and TBI-based conditioning regimen, were obtained from the MSK medical record and transplant database. The presence and severity of acute GVHD (aGVHD) and/or chronic GVHD (cGVHD) were recorded as well [28,29].

Table 1
Characteristics of the Study Participants (n = 123)

Characteristic	Value
Age at TBI, yr, median (range)	11.8 (1.6-21.9)
Age at last follow-up, yr, median (range)	20.1 (4.0-41.3)
Follow-up since TBI, yr, median (range)	8.0 (1.01-24.6)
Sex, n (%)	
Male	77 (62.6)
Female	46 (37.3)
Race, n (%)	
White, non-Hispanic	96 (78.0)
Other	23 (18.6)
No response	4 (.03)
TBI dose	
Range, Gy	12-15
≤1410 cGy, n (%)	54 (43.9)
>1410 cGy, n (%)	69 (56.1)
Primary diagnosis, n (%)	
ALL/NHL	77 (62.6)
AML/CML	46 (37.4)
Pretransplantation therapy, n (%)	
Anthracyclines	115 (93.5)
Glucocorticoids*	100 (81.3)
Cranial radiotherapy	38 (30.9)
Pretransplantation BMI, n (%)	
Obese	20 (16.3)
Nonobese	103 (83.7)
HCT type, n (%)	
Autologous	5 (4.1)
Allogeneic	118 (95.9)
Graft source, n (%)	
Bone marrow	86 (69.9)
Peripheral blood stem cells	27 (21.9)
Cord blood	8 (6.5)
Bone marrow + cord blood	1 (.8)
Bone marrow + peripheral blood stem cells	1 (.8)
Donor source, allogeneic transplants only, n (%)	
Related	59 (50.0)
Unrelated	59 (50.0)
GVHD prophylaxis†, allogeneic transplants only, n (%)	
T cell depletion	77 (65.3)
Cyclosporine	35 (29.7)
Methotrexate	28 (23.7)
Mycophenolate mofetil	8 (6.7)
Corticosteroids	6 (5.2)
Tacrolimus	5 (4.3)
Sirolimus	1 (.9)
Acute GVHD, allogeneic transplants only, n (%)	
Grade I or none	104 (88.1)
Grade II-IV	14 (11.8)
Chronic GVHD, allogeneic transplants only, n (%)	
No	107 (90.7)
Yes	11 (9.3)

TBI indicates total body irradiation; HCT, hematopoietic stem cell transplantation; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; BMI, body mass index; GVHD, graft-versus-host disease.

* Refers to glucocorticoids used for upfront chemotherapy.

† Numbers do not sum to 100%, because most allogeneic HCT recipients received multiple agents for GVHD prophylaxis.

Outcome Measurements

For this analysis, the CVRFs of interest included elevated blood pressure, elevated triglycerides (TG), low high-density lipoprotein (HDL) cholesterol, elevated fasting glucose, and obesity. Waist circumference was not routinely recorded in the medical record.

Individual CVRFs were defined according to current adult International Diabetes Foundation Consensus criteria, as well as pediatric-adapted values when indicated [30], which have been used in previous analyses of CVRFs in childhood cancer survivors [31]. Table 2 summarizes pediatric- and adult-specific criteria used to define each CVRF in the present analysis.

For each participant, serial measurements of height, weight, and blood pressure were abstracted from the medical record. Normative pediatric data were used to calculate age- and sex-specific body mass index [32] for those aged 2 to 20 years, and age-, sex-, and height-specific blood pressure