CLINICAL RESEARCH

Increased Cardiometabolic Traits in Pediatric Survivors of Acute Lymphoblastic Leukemia Treated with Total Body Irradiation

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Survivors of childhood acute lymphoblastic leukemia (ALL) may face an increased risk of metabolic and cardiovascular late effects. To determine the prevalence of and risk factors for adverse cardiometabolic traits in a contemporary cohort of pediatric ALL survivors, we recruited 48 off-therapy patients in remission treated with conventional chemotherapy and 26 treated with total body irradiation (TBI)-based hematopoietic cell transplantation (HCT) in this cross-sectional pilot study. At a median age of 15 years (range, 8-21 years), HCT survivors were significantly more likely than non-HCT survivors to manifest multiple cardiometabolic traits, including central adiposity, hypertension, insulin resistance, and dyslipidemia. Overall, 23.1% of HCT survivors met the criteria for metabolic syndrome (≥3 traits), compared with 4.2% of non-HCT survivors ($P = .02$). HCT survivors also had increased C-reactive protein and leptin levels and decreased adiponectin, suggestive of underlying inflammation and increased visceral fat. In multivariate analyses, history of HCT remained associated with ≥2 traits (odds ratio [OR]. 5.13; 95% confidence interval [CI], 1.54-17.15) as well as with ≥3 traits (OR, 16.72; 95% CI, 1.66-168.80). Other risk factors included any cranial radiation exposure and family history of cardiometabolic disease. In summary, pediatric ALL survivors exposed to TBI-based HCT as well as to any cranial radiation may manifest cardiometabolic traits at an early age and should be screened accordingly.

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INTRODUCTION

The cure rate of childhood acute lymphoblastic leukemia (ALL) now exceeds 85%, resulting in a growing cohort of long-term survivors who potentially face adverse long-term health sequelae as a result of their cancer therapy [1]. There is evidence that ALL survivors treated with conventional therapy alone or with hematopoietic cell transplantation (HCT) are at increased risk of developing multiple related cardiovascular/metabolic risk factors, inluding obesity, hypertension, dyslipidemia, and insulin resistance [2-6]. Together, these components make up the metabolic syndrome, which is associated with a significantly increased risk of both atherosclerotic cardiovascular disease and diabetes mellitus [7-9]. Among ALL survivors, risk may be increased secondary to growth hormone deficiency occurring after cranial radiotherapy and total body irradiation (TBI), which has been associated with obesity and dyslipidemia [3,10]. Because chronic inflammation may have an important role in mediating obesity, insulin resistance, and related cardiovascular diseases [11], chronic graft-versus-host disease (cGVHD) posttransplantation also may increase the risk in affected survivors [12,13]. Other exposures, such as high-dose glucocorticoids (as part of both primary leukemia treatment and GVHD treatment) and more widespread use of immunosuppressive medications, such as calcineurin inhibitors used to prevent or treat GVHD, also have been associated with obesity, hypertension, and dyslipidemia [14,15].

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Because current ALL therapy is characterized by reduced use of cranial radiotherapy and increased use of more-intensive chemotherapy, including more potent glucocorticoids, we conducted this prospective cross-sectional pilot study to determine the prevalence of and risk factors for cardiometabolic traits in pediatric ALL survivors treated since 1990 with conventional chemotherapy and with HCT. We hypothesized that childhood HCT survivors would be at increased risk for these traits compared with ALL survivors treated without HCT, and that this risk would be further modified by a history of GVHD and cranial radiotherapy exposure. In exploratory analysis, we also measured selected cytokines in an attempt to determine whether levels of cytokines associated with inflammation, adiposity, and endothelial dysfunction would be altered in survivors with multiple cardiometabolic traits.

SUBJECTS AND METHODS

Subjects

Eligible subjects for this prospective cross-sectional study were diagnosed with ALL at age <22 years; treated at Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, or Vanderbilt Children's Hospital between 1990 and 2008; and currently aged 8-21 years. Two patient cohorts were recruited, one consisting of individuals in first complete remission after treatment with conventional chemotherapy and the other consisting of individuals treated with HCT, currently in remission, and off any immunosuppressive therapy for GVHD. All subjects had to be at least 1 year off therapy or out from the date of HCT. Subjects were recruited in Seattle between July 2007 and June 2009 and in Nashville between April and June 2009. Among the 41 HCT and 83 non-HCT patients approached for this study, 63.4% and 66.3%, respectively, were enrolled. Seven enrolled non-HCT patients were subsequently excluded (because of Down syndrome in 3 and incomplete data in 4). Final data analysis included 26 HCT and 48 non-HCT survivors. The Institutional Review Boards at all participating centers approved the study protocol, and all participants/guardians provided written informed consent before participation.

Exposure and Outcome Measurements

Medical records were abstracted for previous chemotherapy and radiotherapy doses, including those associated with HCT, history of extensive or moderate/severe cGVHD, and any clinician-reported growth hormone deficiency. Medical histories were updated for any patient who was not seen within the previous year at one of the participating centers. Participants and their parents also completed questionnaires on physical activity [16], diet/food frequencies [17], and family history of cardiovascular disease (ie, coronary heart disease, stroke, hypertension, dyslipidemia) and/or diabetes [18]. Positive family history was defined as having a first-degree relative with the relevant disease.

Height, weight, and waist and hip circumferences were measured, and body mass index (BMI) and waist-to-hip ratio were calculated. Resting blood pressure was measured twice, with a third measurement obtained if systolic or diastolic pressures were >10 mm Hg apart; the most extreme measurement was excluded. Pediatric normative data were used to determine BMI z score [19], waist circumference [20], and blood pressure percentiles [21].

At the same research visit, when possible, following an 8-hour overnight fast, blood samples were obtained for a lipid profile (total cholesterol, high-density lipoprotein [HDL], and triglycerides), glucose, insulin, and selected cytokines (leptin, adiponectin, high sensitivity C-reactive protein [CRP], interleukin [IL]-6, tumor necrosis factor [TNF]-α, E-selectin, and soluble intercellular and vascular cell adhesion molecules [sICAM, sVCAM]). Lipid profiles were collected and processed at the participating institutions' hospital laboratories. Glucose was measured using an automated hexokinase method (Roche Diagnostics, Indianapolis, IN), and insulin was measured using an automated immunoenzymometeric assay (Tosoh Bioscience, San Francisco, CA). Cytokines were collected and processed under a standardized protocol [22] and then stored at -80°C before being batch analyzed using a commercially available fluorokine multianalyte profiling kit (R&D Systems, Minneapolis, MN) on a Luminex 200 analyzer (Luminex, Austin, TX). As a measure of insulin resistance, the homeostasis model assessment (HOMA) was calculated from fasting glucose and insulin values [23], based on the following formula: glucose (mmol/L) $\times$ insulin (mU/L)/22.5.

Cardiometabolic traits were defined a priori via current adult International Diabetes Foundation Consensus criteria [9] for subjects aged $\geq$18 years and pediatric-adapted values for those aged <18 years (Table 1). Sensitivity analysis used criteria based on the older but still widely used National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines [7,8], with a fasting glucose level $\geq$100 mg/dL defined as abnormal. For this study, we tabulated the number of abnormal components present in each individual and categorized individuals as having the metabolic syndrome if any 3 or more of the 5 criteria were present.

Statistical Analyses

Continuous parameters with skewed distributions were transformed when possible. Differences in