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Vascular Structure and Function in Cancer Survivors after Hematopoietic Stem Cell Transplantation

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A B S T R A C T

This study examined the effects of hematopoietic cell transplantation (HCT) and associated preparative regimens on vascular structure and function. Measures of carotid artery stiffness and brachial artery endothelial-dependent dilation were obtained in patients who had survived ≥ 2 years after HCT for hematologic malignancy and were diagnosed at ≤21 years. HCT survivors (n = 108) were examined: 66 received total body irradiation (TBI) alone or with a low-dose cranial radiation boost (TBI±LD-CRT), 19 received TBI plus high-dose cranial radiation (TBI+HD-CRT), and 23 received a chemotherapy-only preparative regimen (CHEMO). Siblings (n = 83) were invited to participate as control subjects. Although endothelial-dependent dilation did not differ between siblings and HCT survivors, carotid cross-sectional compliance, cross-sectional distensibility, diameter compliance, and diameter distensibility were greater in siblings than HCT survivors. Comparing the HCT preparative regimens, carotid cross-sectional compliance, cross-sectional distensibility, diameter compliance, diameter distensibility, and incremental elastic modulus were significantly lower in the TBI+HD-CRT group compared with siblings or with TBI± LD-CRT and CHEMO treatment groups. Cross-sectional distensibility and diameter compliance were significantly lower in the TBI±LD-CRT group compared with siblings. TBI±LD-CRT and CHEMO groups did not differ from each other in these vascular measures. HCT preparative regimens containing TBI+HD-CRT resulted in greater arterial decrements, indicating increased risk for cardiovascular disease.

INTRODUCTION

Although the incidence of cancer diagnoses in children has remained constant over the last few decades, survival has increased to a 5-year rate of 83% in 2003 to 2009 [1]. One of the main reasons for this improvement is major advances in treatment that were implemented during this period [2,3]. One such advance is the use of hematopoietic cell transplantation (HCT), which has been shown to be effective for several high-risk and relapsed hematologic malignancies. Over 80% of those who survive the first 2 years of HCT treatment are expected to be long-term survivors [4,5]. However, HCT survivors are at increased risk for a variety of chronic conditions and impairments involving virtually every organ system [6]. The risk of these complications is influenced by pretransplantation treatment exposures and transplantation-related conditioning regimens and by development of post-transplantation graft-versus-host disease (GVHD).

To date, most studies examining cardiovascular risk in cancer survivors have focused on adult survivors of childhood cancer who have undergone chemotherapy and/or body irradiation [7-9]. Few if any studies have examined the effect on carotid vascular structure and function among childhood cancer survivors who underwent HCT and were conditioned with total body irradiation (TBI) and/or chemotherapy. Stiffening of arteries impairs the ability of the arterial system to handle the spontaneous elevation in blood pressure at systole, which leads to increased systolic blood pressure and left ventricular afterload with a subsequent increase in myocardium mass and decreased diastolic blood pressure and diastolic coronary perfusion. Therefore, assessment of arterial compliance and distensibility of large conduit arteries such as the carotid artery is a technique widely used to assess vascular elasticity and arterial stiffness and overall vascular health [10]. Therefore, this study's primary objective was to evaluate measures

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of brachial and carotid artery structure and function in a relatively large population of young adult childhood cancer survivors who received HCT as part of their treatment regimens when they were children and to compare their results with a control group of healthy siblings.

METHODS

The study protocol was approved by the Institutional Review Board and complied with Health Insurance Portability and Accountability Act guidelines. All subjects submitted written informed consent and assent (when appropriate) for study participation.

Study Population

HCT databases at the University of Minnesota and the Fred Hutchinson Cancer Research Center identified all HCT recipients who were transplanted for a hematologic malignancy between 1975 and 2008 and who had survived at least 2 years post-HCT. In addition, participants had to be younger than age 22 years at diagnosis and at least 10 years old at the time of study entry to comply with the study procedures. In total, 557 subjects were potentially eligible. Twenty-six of those were deemed ineligible because of active GVHD or disease status not in remission, and 84 had previously been listed in the databases as known lost to follow-up or had requested "Do Not Contact" research status, leaving an eligible population of 447 subjects. Eligible subjects were randomly ordered and recruited in sequential blocks of 20. If a sampled individual within a block declined to participate or could not be contacted after several attempts, the next ordered individual in that block was approached for recruitment until study enrollment was completed, which occurred after attempted contact with the first 339 subjects. Of these 339 subjects, 60 refused participation, and we were unable to establish contact with 125 others after at least 3 attempts. Of the remaining 154 subjects who were recruited (overall participation rate of 45%, 72% of those who were successfully contacted), 3 were found to be ineligible at the time of study becasue of previously undiagnosed diabetes (n = 1), severe hypertension (n = 1), and multiple medical issues (n = 1) that all required immediate medical treatment so that they were unable to complete any study procedures. This left the final study population of 151 subjects. Because of limitations in ultrasound imaging equipment and qualified sonographers, only subjects (and their siblings) enrolled at the University of Minnesota were eligible to have vascular assessments performed, providing 108 cases with completed vascular assessments for inclusion in this analysis (Figure 1).

All 108 patients received myeloablative preparative regimens. Sixty-six (61%) received TBI with or without low-dose cranial radiation boost (TBI±LD-CRT), whereas 19 patients (18%) received TBI with high-dose (HD) CRT (TBI +HD-CRT) given either before or concurrent with TBI in all cases. TBI was delivered in fractionated doses for all cases with the exception of 3 cases in the TBI+HD-CRT group and 10 cases in the TBI±LD-CRT group who received a single-fraction TBI dose between 750 and 850 cGy. One additional patient in the TBI±LD-CRT group received 200 cGy of single-fraction TBI for an allogeneic HCT that followed a prior failed autologous HCT for Hodgkin disease. Twenty-three patients (21%) received chemotherapy only (CHEMO group), with most busulfan based. Transplants were performed for acute lymphoblastic leukemia or non-Hodgkin lymphoma in 41 patients (38%), acute or chronic myeloid leukemia or myelodysplastic syndrome in 57 patients (53%), and Hodgkin lymphoma in 10 patients (9%).

The control group consisted of eligible healthy siblings who were ≥10 years old at study entry and who had never had a malignancy or HCT. Based on a predetermined frequency matched enrollment scheme, siblings were recruited with the intent to represent the age and sex distribution of HCT recipients. Selection of the sibling closest in age to the subject was preferred, although not required, and having a sibling was not a requirement for participation. Siblings were chosen as the control population to obtain greater similarity to HCT recipients in genetics, lifestyle, and environment/geographic trends. Because of larger differences in age between siblings and the HCT survivor group and the sibling control group, a sensitivity analysis was done to create a sibling control group that was closer in age to the HCT survivor group. To create the age-appropriate sibling control group the HCT survivor group was divided by age into the 20th, 40th, 60th, 80th, and > 80th percentiles. The sibling control group was than divided into 5 groups using the age quintiles computed in the HCT survivor group. Those siblings who fit into the HCT survivor age quintiles were than used as the sibling control group (n = 83).

Measurements

Anthropometric and blood pressure assessments

Measurements for height and weight were taken at the start of the visit, and body mass index was calculated as weight in kilograms divided by height in meters squared. Seated blood pressure was obtained in the right arm using an automatic blood pressure monitor (model BP-8800C; Colin Press-Mate, San Antonio, TX). Tanner stage was assigned according to pubic hair development in boys and breast and pubic hair development in girls.

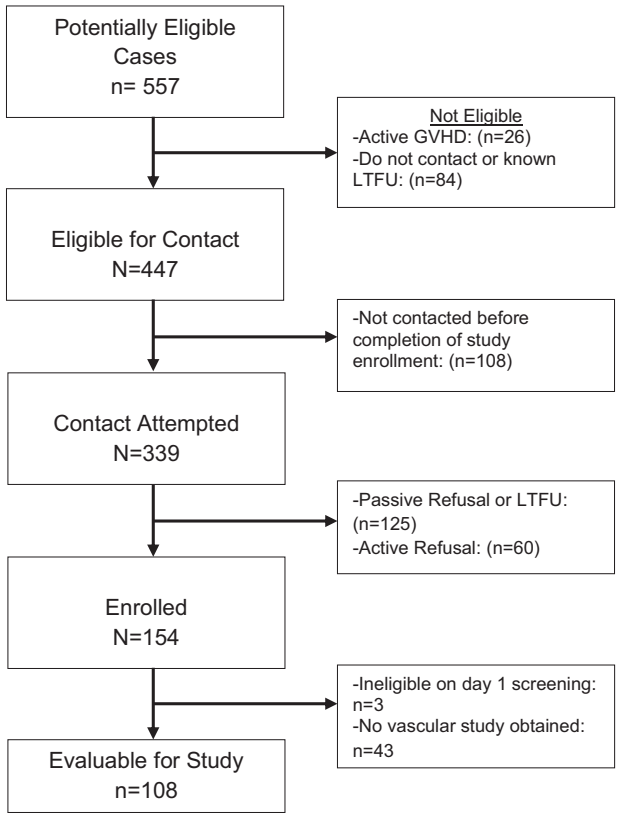

Figure 1. CONSORT diagram.

Vascular assessments

All vascular testing was performed after a 15-minute rest period in a quiet, temperature-controlled environment (22° to 23°C) with the subject in the supine position. Artery images were measured using a conventional ultrasound scanner (Acuson, Sequoia 512; Siemens Medical Solutions USA, Inc., Mountain View, CA) with a 15-8 MHz linear array probe. All images were digitized and stored on a personal computer for later off-line analysis of arterial compliance and distensibility. Electronic wall-tracking software was used for the analysis (Vascular Research Tools 5; Medical Imaging Application, LLC, Iowa City, IA).

For imaging of the carotid artery the ultrasound transducer was held 1-cm proximal from the carotid bifurcation bulb, to measure the carotid intima-media thickness (cIMT) and to capture the left common carotid artery's lumen diastolic and systolic diameters. Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer during the 10-second carotid measurements. The ultrasound scanning system was interfaced with a standard personal computer equipped with a data acquisition card to obtain radiofrequency ultrasound signals from the scanner. Images were collected at 20 frames per second for 10 seconds (200 frames) to ensure capture of the full arterial diameter change during a cardiac cycle. The mean diameter through the 10-second cycle was used to calculate measures of carotid vessel function. Briefly, the following formulas were used to measure carotid distensibility and compliance in the cross-sectional and longitudinal planes:

- Diameter distensibility (%) is defined as [(maxDiamM − minDiamM)/minDiamM] × 100%
- Cross-sectional distensibility (%) is defined as $[(\pi \times (\text{maxDiamM}/2)^2 - \pi \times (\text{minDiamM}/2))/\pi \times (\text{minDiamM}/2)] \times 100\%$
- Diameter compliance (mm/mm Hg) is defined as [(maxDiamM − minDiamM)/ΔP]
- Cross-sectional compliance (mm^2 mm Hg] is defined as $[(\pi \times (\text{maxDiamM}/2)^2 - \pi \times (\text{minDiamM}/2)^2)/(\Delta P)]$

- Incremental elastic modulus (mm Hg) is defined as $3\{1+[\pi \times (\text{maxDiamM}/2)^2/\pi \times (\text{minDiamM}/2)/\text{cross-sectional compliance}$

where ΔP is pulse pressure, calculated as the difference between systolic and diastolic pressures; maxDiamM is maximum diameter measurement; and minDiamM is minimum diameter measurement.

After measuring carotid structure and function, flow-mediated endothelial-dependent dilation was assessed by imaging the left brachial artery at the distal third of the upper arm using techniques previously described by our laboratory and others [11,12]. A blood pressure cuff was inflated below the elbow to a pressure of 200 mm Hg and maintained for 5 minutes to induce muscle ischemia. Brachial artery diameter was measured continuously for a 3-minute period immediately after cuff release during reactive hyperemia to determine peak endothelial-dependent dilation (the greatest percent change from resting baseline brachial artery diameter after reactive hyperemia during the 3-minute collecting period). After a 15-minute rest .3 mg sublingual nitroglycerin was administered, and the diameter of the brachial artery was continuously measured for a 15-minute period after nitroglycerin administration. Peak nitroglycerin-mediated endothelial-independent dilation was defined as the highest percent change from resting baseline brachial artery diameter after nitroglycerin administration. Reproducibility of the cIMT and endothelial-dependent dilation techniques in healthy young adults in our laboratory showed a mean difference of .02 ± .03 mm and .39% ± .65%, respectively, for analysis separated by 1 week [13].

All patients undergo standardized GVHD assessments and data reporting as part of the standardized process for data collection in the institutional Bone Marrow Transplant database for both acute and chronic GVHD. All case report forms are reviewed and evaluated by a single individual for confirmation of GVHD and scoring before database entry. Because of the potential impact on study outcomes from steroids and other GVHD therapies, no subjects with active GVHD requiring therapy were enrolled.

Statistical Analysis

Descriptive statistics are expressed as frequencies, percent, or mean ± standard error, as appropriate. For unadjusted comparisons among HCT groups but not control subjects, *P* values were calculated using the *t*-test or Fisher's exact test; for unadjusted comparisons involving HCT groups and sibling control subjects, *P* values were calculated from generalized estimating equations with robust standard errors, accounting for clustering by sibship of cases and control subjects. Multivariable linear regression models were used to compare groups according to adjusted mean outcome measures, with adjustments for age, sex, race, and Tanner stage unless noted otherwise. *P* values and *P* value thresholds were not adjusted for multiple comparisons. All analyses used the SAS system (version 9.2; SAS Institute, Cary, NC).

RESULTS

Table 1 describes the study population's demographic characteristics. There were no significant differences in race/ethnicity between the HCT survivors as a whole group and the sibling control subjects. Despite the frequency matching and the selection scheme for siblings, HCT survivors were slightly older compared with their sibling control subjects. However, the proportion of males to females and Tanner state were similar for the HCT survivors and sibling control subjects. The HCT survivor group was shorter in stature and had lower weight than the sibling control group, although body mass index did not differ significantly between HCT survivors and sibling control subjects (Table 2). Although systolic blood pressure did not differ between the HCT survivors and the sibling control subjects, diastolic blood pressure was significantly higher in the HCT survivors (Table 2).

The physical characteristics of the study population, divided according to treatment group, are described in Table 2. Patients who received TBI±LD-CRT or TBI+HD-CRT were significantly shorter and weighed less than the sibling control subjects. As a result the TBI±LD-CRT group had body mass indices significantly lower than the sibling control group (Table 2). No differences in blood pressure were noted among the HCT treatment groups, except the TBI±LD-CRT and TBI +HD-CRT groups had significantly higher diastolic blood pressure than the sibling control group (Table 2).

Table 3 shows measures of carotid structure and function as well as brachial artery reactivity. Analyses of vascular measures were adjusted for age at study, sex, race, and Tanner score. Although lumen diameter was significantly smaller in HCT survivors as a whole compared with sibling control subjects, cIMT did not differ significantly between HCT survivors and sibling control subjects. Also, cIMT did not differ significantly between the various HCT treatment groups. Carotid cross-sectional distensibility, carotid diameter compliance, and carotid diameter distensibility were significantly lower in HCT survivors than in sibling control subjects. The carotid cross-sectional distensibility, diameter compliance, diameter distensibility, and incremental elastic modulus were significantly lower in the TBI +HD-CRT group compared with the sibling control subjects and the TBI±LD-CRT and CHEMO groups. Cross-sectional distensibility and diameter compliance were significantly lower in those groups using TBI compared with the sibling control subjects. The TBI±LD-CRT and CHEMO groups did not differ from each other in these vascular measures. Measures of brachial artery function (ie, endothelial-dependent dilation and endothelial-independent dilation) were corrected for brachial artery diameter; they did not differ significantly between HCT survivors as a whole and the sibling control subjects or between the 3 HCT survivor groups.

Table 4 contains information regarding treatment and time since treatment. The 3 treatment groups did not differ significantly in years post-transplant. A greater percentage of the CHEMO group received autologous bone marrow transplant compared with the 2 other treatment groups. As a result fewer

Table 1
Demographic Characteristics between HCT Survivor Groups and Sibling Control Subjects

	Siblings(n = 83)	HCT Survivors(n = 108)	TBI+HD-CRT Group(n = 19)	TBI±LD-CRT Group(n = 66)	CHEMO Group(n = 23)
Age (yr)	22.20 ± .92	26.36 ± .90 *P* = .0002	25.19 ± 1.63 *P* = .11	26.33 ± 1.28 *P* = .0026	27.42 ± 1.53 *P* = .0028
Sex, male/female (% male)	45/38 (54)	66/42 (61) *P* = .27	13/6 (68) *P* = .25	42/24 (64) *P* = .20	11/12 (48) *P* = .69
Race/ethnicity					
White non-Hispanic	75 (90)	100 (93) *P* = .45	17 (89) *P* = .89	63 (95) *P* = .17	20 (87) *P* = .68
Others	8 (10)	8 (7)	2 (11)	3 (5)	3 (13)
White Hispanic	1 (1)	2 (2)	1 (5)	0 (0)	1 (4)
Black	1 (1)	4 (4)	1 (5)	2 (3)	1 (4)
Others	6 (7)	2(1)	0 (0)	1 (2)	1 (4)
Tanner Stage 4-5	72 (90)	87 (88) *P* = .64	16 (84) *P* = .46	51 (86) *P* = .50	20 (95) *P* = .45

Values are mean ± standard error or n (%). *P* values reflect comparison of that treatment group vs. sibling control group.

Table 2
Comparison of Body Composition Measures between HCT Survivor Groups and Sibling Control Subjects

	Siblings(n = 83)	HCT Survivors(n = 108)	TBI+HD-CRT Group(n = 19)	TBI±LD-CRT Group(n = 66)	CHEMO Group(n = 23)
Height, cm	171.63 ± .89	163.95 ± .94 <.0001	161.42 ± 1.96 <.0001[a]	162.26 ± 1.12 <.0001[a]	170.98 ± 1.78 .72
Weight, kg	71.19 ± 1.44	62.27 ± 1.88 .0002	58.79 ± 3.96 .0022[a]	59.24 ± 1.84 <.0001[a]	73.48 ± 5.25 .70
Body mass index, kg/m^2	23.91 ± .39	22.83 ± .56 .107	22.34 ± 1.36 .24[a]	22.25 ± .59 .0165[a]	24.77 ± 1.50 .59 [a]
SBP, mm Hg	116.07 ± 1.39	116.24 ± 1.42 .93	125.25 ± 4.66 .0626	113.59 ± 1.48 .21[a]	114.87 ± 2.35 .66 [a]
DBP, mm Hg	61.77 ± 1.00	66.70 ± 1.11 .0016	70.47 ± 3.44 .0169[a]	65.88 ± 1.26 .0146[a]	65.38 ± 1.41 .0523[a]

Values are mean ± standard error and are adjusted for age at study, sex, race, and Tanner score. *P* values reflect that treatment group vs. sibling control group. If treatment groups do not share a letter within the same row they are significantly different ($P < .05$).

subjects in the CHEMO group were at risk for GVHD compared with the other 2 groups, and indeed fewer had any GVHD. When the comparisons in Table 3 were adjusted for GVHD, age at study, sex, race, and Tanner score, the only notable change was that cIMT was significantly lower in the CHEMO group compared with the TBI+HD-CRT group (adjusted average ± standard error, .46 ± .01 versus .50 ± .01 mm; $P = .05$) but was not different compared with the TBI±LD-CRT group (.047 ± .01 mm, $P = .08$). In addition, systolic blood pressure was significantly higher in the TBI+HD-CRT group (123.36 ± 4.56 mm Hg) compared with both the TBI±LD-CRT (111.71 ± 1.48 mm Hg, $P < .0001$) and CHEMO (112.69 ± 2.34 mm Hg, $P = .006$) groups. Diastolic blood pressure was also higher in the TBI+HD-CRT group compared with the TBI±LD-CRT group (68.73 ± 3.45 versus 64.09 ± 1.25 mm Hg, $P = .04$) but was not different compared with the CHEMO group (63.52 ± 1.51 mm Hg, $P = .065$).

DISCUSSION

Measures of vascular endothelial function, stiffness, and cIMT are important early markers of subclinical atherosclerosis and increased cardiovascular disease risk [14-17]. To our knowledge this is the first study to examine the effect of HCT and associated pre-HCT conditioning regimens (chemotherapy alone or combined with TBI, with or without additional central nervous system irradiation) on measures of vascular structure and function in childhood cancer survivors.

In the present study HCT survivors as a whole displayed increased carotid artery stiffness compared with healthy sibling control subjects. This observation is consistent with the results of Vatanen et al. [18] and Turanlahti et al. [19], who both reported reduced carotid vascular function in HCT survivors. In the present study HCT survivors who received both TBI and central nervous system irradiation had significantly lower measures of carotid vascular function than HCT survivors who received the other 2 treatments. These results differ somewhat from those reported by Vatanen et al. [18], who did not find any difference in carotid vascular function between HCT survivors who received TBI and HCT survivors who did not. One explanation for the differences between the present study and Vatanen et al. [18] may be the number of patients studied. Vatanen et al. [18] studied only 19 total HCT survivors, 9 who

Table 3
Comparison of Brachial and Carotid Vascular Measures between HCT Survivor Groups and Sibling Control Subjects

	Siblings (n = 83)	HCT Survivors (n = 108)	TBI+HD-CRT Group (n = 19)	TBI±LD-CRT Group (n = 66)	CHEMO Group (n = 23)
Measures of vascular function					
EDD, %	7.48 ± .40	6.97 ± .39 .39	7.10 ± 1.06 .73	6.45 ± .43 .11	8.24 ± .86 .44
EID, %	24.34 ± .67	23.46 ± .60 .34	23.38 ± 1.30 .50	23.74 ± .86 .62	22.79 ± .89 .14
CSC, mm^2 mm Hg^{-1}	0.51 ± .02	0.46 ± .02 .0548	0.41 ± .05 .0613	0.47 ± .02 .17	0.49 ± .04 .70
cDC, mm/mm Hg × 100	1.43 ± .04	1.29 ± .04 .02	0.96 ± .07 <0.0001	1.36 ± .05[a] .36	1.40 ± .09[a] .75
CSD, %	27.40 ± .74	22.30 ± .66 <0.0001	18.91 ± 1.66 <0.0001	22.59 ± .76[a] <0.0001	24.83 ± 1.26[a] .0788
DD, %	12.81 ± .33	10.54 ± .29 <0.0001	8.99 ± .75 <0.0001	10.68 ± .34[a] <0.0001	11.69 ± .56[a] .0867
IEM, mm Hg	1166.0 ± 57.5	1276.1 ± 52.8 .19	1745.5 ± 172.3 .0014	1187.8 ± 50.0[a] .75	1076.4 ± 83.1[a] .45
Measures of vascular structure					
Brachial diameter, mm	3.64 ± .05	3.40 ± .04 .0003	3.34 ± .11 .0125	3.39 ± .05 .0005	3.49 ± .09 .14
cLD, mm	6.15 ± .06	5.76 ± .05 <0.0001	5.64 ± .10 <0.0001	5.80 ± .08 .0002	5.75 ± .08 <0.0001
cIMT, mm	0.46 ± .005	0.47 ± .006 .18	0.50 ± .025 .095	0.47 ± .007 .28	0.45 ± .015 .61

All measures (mean ± standard error) except EDD, EID, and cIMT are adjusted for age at study, sex, race, and Tanner score. EDD and EID are adjusted for age at study, sex, race, Tanner score, and brachial artery diameter. cIMT is adjusted for age at study, sex, race, Tanner score, and lumen diameter. *P* values reflect comparison of that treatment group vs. sibling control group. If treatment groups do not share a letter within the same row they are significantly different ($P < .05$). EDD indicates endothelial-dependent dilation; EID, endothelial-independent dilation; DD, diameter distensibility; CSD, cross-sectional distensibility; DC, diameter compliance; CSC, cross-sectional compliance; IEM, incremental elastic modulus; cLD, carotid lumen diameter.

Table 4
Treatment and Survival Information

Variable	TBI+HD-CRT Group(n = 19)	TBI±LD-CRT Group(n = 66)	CHEMO Group(n = 23)	*P*
Years post-transplant, mean ± standard error	15.71 ± 1.78	14.58 ± .93	13.69 ± 1.11	.67
Types of bone marrow transplant*				
Allogeneic	15 (79)	58 (88)	7 (30)	
Autologous	4 (21)	8 (12)	15 (70)	<.0001
GVHD*	8 (42)	34 (52)		
Yes	11 (58)	32 (48)	3 (13)	
No			20 (87)	.0038
TBI dose†				
Median, cGy	1320	1320		
Range, cGy	750-1375	200-1375	na	.68
Cranial radiation‡	(n = 19)	(n = 8)		
Median dose, cGy	2340	600		
Range, cGy	1500-3600	300-600	na	<.0001

Values are n (%) unless otherwise defined. na indicates.
*Both TBI groups are statistically significantly different from the CHEMO group (p-value<0.05).
†*P* compares TBI+HD-CRT with TBI±LD-CRT.
‡$P < .05$ vs. CHEMO.

did not receive TBI and 10 who did. Also, none of the patients studied by Vatanen et al. [18] received central nervous system irradiation in conjunction with TBI. It may be that additional radiation scatter field exposure received during central nervous system irradiation results in greater decrement in carotid vascular function. The finding of no difference in carotid vascular function between the TBI and chemotherapy-only treatment groups would support the hypothesis that the addition of central nervous system irradiation results in further damage to the carotid artery.

Although we found significant differences in carotid vascular function between HCT survivors and healthy sibling control subjects, we did not find any structural differences as evidenced by the lack of significant differences in cIMT, whether examined in the entire cohort of HCT survivors or separated by treatment. These results are similar to a previous study by our group [13] in childhood cancer survivors who survived ≥ 5 years after diagnosis of leukemia, lymphoma, central nervous system tumor, or sarcoma. In that study we observed lower carotid vascular function in survivors of leukemia compared with their sibling control subjects but no difference in cIMT. Like the present study, Turanlahti et al. [19] also did not find any difference in cIMT between HCT survivors and healthy control subjects. It should be noted that Vatanen et al. [18] reported greater cIMT in HCT survivors than healthy control subjects, but when the HCT survivors were analyzed by treatment (ie, those who received TBI and those who did not), no significant difference in cIMT was observed between these 2 HCT treatments and healthy control subjects.

Surprisingly, even though we observed significantly reduced carotid vascular function in the present study, we did not find reductions in brachial artery endothelial-dependent or −independent dilation in patients who had undergone HCT compared with healthy sibling control subjects. In our previous studies of childhood cancer survivors [13,20] we observed significant decreases in both brachial artery endothelial-dependent dilation [13,20] and brachial artery endothelial-independent dilation [20]. Those previous studies differed from the current study mainly in that no subjects in the previous studies underwent HCT. In the initial study [20] we examined brachial artery function in young adult survivors of childhood acute lymphoblastic leukemia and observed that patients who received chemotherapy had significant reductions in both endothelial-dependent and -independent brachial dilation compared with healthy control subjects. Adding radiation to the chemotherapy regimen did not result in any further decrements in brachial artery endothelial-dependent or -independent brachial dilation. In the other study [13] we examined brachial artery function in 319 childhood cancer survivors who survived for ≥5 years after diagnosis of leukemia, lymphomas, central nervous system tumors, or sarcomas. Endothelial-dependent dilation was significantly lower in leukemia survivors compared with healthy sibling control subjects, whereas there was no difference in endothelial-dependent dilation between central nervous system tumor and sarcoma survivors and healthy sibling control subjects. Endothelial-independent dilation did not differ significantly between healthy sibling control subjects and childhood cancer survivors as a whole or individual diagnosis groups. In that study [13] all leukemia survivors had undergone chemotherapy but few received radiation (14%). Some survivors of central nervous system tumors (32%) and solid tumors (29%) also received radiation, but most irradiation was localized to the tumor site. However, in that study [13] it was hard to attribute changes in vascular structure and function to 1 particular treatment exposure because of significant differences in the treatment protocols received.

Two other studies [18,19] also reported no significant difference between HCT survivors and healthy control subjects in brachial artery endothelial-dependent dilation. As stated at a National Institutes of Health consensus conference on the late effects of pediatric HCT treatments [5], the degree of cellular damage that occurs in these patients is related to the health status of the pre-HCT recipient, presence of other comorbidities, and baseline organ function of the recipient at the time of the HCT regimen. Other factors such as the intensity of conditioning regimen, infections, drug exposures, and delayed immune intolerance also contribute to the end-organ fibrosis and dysfunction.

It should be noted that the present study has some limitations. The population was predominantly white and non-Hispanic, and therefore the findings may not be generalizable to other racial/ethnic groups. There was a small age difference between the HCT survivors and their healthy sibling control subjects. However, the benefit of using siblings as control subjects is that the environment was the same for both individuals. The statistical analysis was performed controlling for differences between HCT survivors and healthy sibling control subjects, including gender and age differences. Finally, a number of multiple comparisons could have an effect on the final interpretation of the results.

In conclusion, the present study suggests that use of TBI in the HCT regimen has an effect on measures of carotid stiffness. The addition of central nervous system irradiation to TBI may contribute further dysfunction in the carotid arteries. Although it is important for clinicians to monitor cardiovascular health in all HCT survivors, the data from the present study suggest that HCT survivors who received TBI plus CRT might be at even greater risk for cardiovascular disease. These individuals may require an even higher degree of monitoring. The monitoring of HCT survivors' cardiovascular health should include ultrasound imaging of the carotid artery. Measurement of cIMT is routine in most cardiovascular centers. However, as indicated by the results in the present study, ultrasound imaging of the carotid artery should not only include measures of cIMT but should also include measures of carotid function (ie, compliance, distensibility, incremental elastic modulus, etc.). Although measures of carotid function have not been typically done in the past, many new ultrasound scanners can automatically calculate these measures of carotid function. However, even if cardiovascular centers are using an older ultrasound scanner that does not have the necessary software, these measures can be easily calculated using the formulas provided in the vascular assessments section.

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SUPPLEMENTARY DATA

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