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Brief Article

Association of Chronic Graft-versus-Host Disease with Late Effects following Allogeneic Hematopoietic Cell Transplantation for Children with Hematologic Malignancy

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A B S T R A C T

Chronic graft-versus-host disease (cGVHD) occurs in up to 25% of children following allogeneic hematopoietic cell transplantation (HCT) and continues to be a major cause of late morbidity and poor quality of life among long-term survivors of pediatric HCT. Late effects (LEs) of HCT are well documented in this population, and cGVHD has

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been identified as a risk factor for subsequent neoplasms (SNs) and several nonmalignant LEs (NM-LEs); however, the reported correlation between cGVHD and LEs varies among studies. We compared LEs occurring ≥2 years following childhood HCT for a hematologic malignancy in 2-year disease-free survivors with and without cGVHD and further evaluated the association of cGVHD features on the development of LEs. This systematic retrospective analysis used data from the Center of International Blood and Marrow Transplant Research (CIBMTR) on a large, representative cohort of 1260 survivors of pediatric HCT for hematologic malignancy to compare first malignant LEs and NM-LEs in those with a diagnosis of cGVHD and those who never developed cGVHD. The cumulative incidences of any first LE, SN, and NM-LE were estimated at 10 years after HCT, with death as a competing risk for patients with cGVHD versus no cGVHD. Cox proportional hazards models were used to evaluate the impact of cGVHD and its related characteristics on the development of first LEs. The estimated 10-year cumulative incidence of any LE in patients with and without cGVHD was 43% (95% CI, 38% to 48.2%) versus 32% (95% confidence interval [CI], 28.5% to 36.3%) ($P < .001$), respectively. The development of cGVHD by 2 years post-HCT was independently associated with any LE (hazard ratio [HR], 1.38; 95% CI, 1.13 to 1.68; $P = .001$) and NM-LE (HR, 1.37; 95% CI, 1.10 to 1.70; $P = .006$), but not SN (HR, 1.30; 95% CI, .73 to 2.31; $P = .38$). cGVHD-related factors linked with the development of an NM-LE included having extensive grade cGVHD (HR, 1.60; 95% CI, 1.23 to 2.08; $P = .0005$), severe cGVHD (HR, 2.25; 95% CI, 1.60 to 3.17; $P < .0001$), interrupted onset type (HR, 1.57; 95% CI, 1.21 to 2.05; $P = .0008$), and both mucocutaneous and visceral organ involvement (HR, 1.59; 95% CI, 1.24 to 2.03; $P = .0002$). No significant association between cGVHD-specific variables and SN was identified. Finally, the duration of cGVHD treatment of cGVHD with systemic immunosuppression was not significantly associated with SNs or NM-LEs. cGVHD was more closely associated with NM-LEs than with SNs among survivors of pediatric HCT for hematologic malignancy. In this analysis, the development of SNs was strongly associated with the use of myeloablative total body irradiation. cGVHD-related characteristics consistent with a state of greater immune dysregulation were more closely linked to NM-LEs.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for many high-risk hematologic malignancies of childhood. Although the number of long-term survivors of pediatric HCT continues to grow, children remain at significant risk for organ impairments and adverse health outcomes following transplantation owing to the high-intensity treatment protocols used for curative intent [1,2]. Furthermore, chronic graft-versus-host disease (cGVHD) remains a major risk factor for late morbidity and nonrelapse mortality in children [3–6]. One of the earliest reports arising from the Bone Marrow Transplant Survivor Study and Childhood Cancer Survivor Study identified active cGVHD as a predictor of impaired function, pain, and overall poor health status [7]. Other very early studies reported an adverse association between cGVHD and a host of late effects (LEs) [2]. More recently, cGVHD has been linked to an elevated risk of diabetes mellitus, avascular necrosis, and cataracts among long-term survivors of HCT for adolescent and young adult acute myelogenous leukemia [8]. In that study, cGVHD was not a predictor for subsequent neoplasms (SNs), but this finding might have been related to the relatively short follow-up [8]. In survivors who underwent HCT at age <3 years [4], the occurrence of cGVHD at 1 year was not associated with increased risk of individual late organ toxicities, but this observation might have been limited by low patient numbers. Nonetheless, cGVHD was predictive of increased risk of mortality in this very young population [4].

Because cGVHD occurs in up to 25% of children who undergo HCT [9–11] and given the longer life expectancy of children, there is a pressing need to understand the impact of cGVHD on LEs in this vulnerable population. Risk factors associated with long-term survival in children with cGVHD have been reported [5]; however, the association of certain cGVHD-related factors with LEs has not been examined.

We carried out this large population-based study using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) to determine the cumulative incidence of first malignant LEs and nonmalignant (NM)-LEs occurring ≥2 years post-transplantation, comparing 2-year disease-free survivors of HCT for childhood hematologic malignancy with and without cGVHD. We also studied risk factors for the development of first LEs in survivors with cGVHD.

METHODS

Data Source

The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin that includes more than 450 transplantation centers worldwide who contribute detailed data prospectively on consecutive transplantations to the CIBMTR. All patients are followed longitudinally until death or loss to follow–up. Patients and/or guardian(s) provide written informed consent for data submission and research participation. Compliance and accuracy of data reported to the CIBMTR are monitored by computerized error checks, physician data review, and onsite audits.

Study Population

The study population included children (age 0 to <18 years at HCT) who underwent first allogeneic HCT for any hematologic malignancy using a myeloablative conditioning regimen between 2000 and 2010 and who were alive and disease-free at 2 years after their HCT and were reported to the CIBMTR. Patients who underwent transplantation with all donor types/graft sources were included. Patients were excluded if they had a diagnosis of therapy-related acute myelogenous leukemia or a cancer predisposition syndrome. Patients with a diagnosis of pediatric non-Hodgkin lymphoma, a ≤6/8 HLA-matched unrelated donor, receipt of a reduced-intensity or nonmyeloablative conditioning regimen, or GVHD prophylaxis with post-transplantation cyclophosphamide also were excluded owing to low numbers.

cGVHD, LEs, and Outcomes Definitions

cGVHD and LE data from this patient population were collected through CIBMTR Comprehensive Report Forms that are obtained on a subset of CIBMTR participants selected by weighted randomization for more comprehensive research-level data collection.

Diagnosis of cGVHD grade (limited or extensive) was based on the Seattle criteria [12], because the 2005 National Institutes of Health consensus criteria for cGVHD [13] had not yet been included on CIBMTR forms for this analysis. The CIBMTR definitions of cGVHD severity (mild, moderate, severe), cGVHD onset type (progressive, interrupted, or de novo), and cGVHD organ involvement (mucocutaneous or visceral) were used for this analysis [14]. cGVHD severity reflects the maximum severity documented over longitudinal follow-up as determined by best clinical judgment. Mild cGVHD includes signs and symptoms that do not interfere substantially with function and do not progress once appropriately treated. Moderate cGVHD interferes somewhat with function despite appropriate therapy or progress through first-line systemic therapy. Severe cGVHD substantially limits function despite appropriate therapy or progresses through second-line therapy. The CIBMTR definition for cGVHD onset type is relative to the timing of acute GVHD (aGVHD) and is classified as progressive (aGVHD present within 2 weeks of cGVHD diagnosis), interrupted (aGVHD resolved >2 weeks prior to cGVHD

onset), or de novo (aGVHD never developed prior to cGVHD). Finally, the duration of immunosuppression was defined as the duration of treatment for cGVHD using systemic steroid and nonsteroid immunosuppression and was categorized as duration of <12 months versus ≥12 months.

The following LEs and their date of diagnosis were captured: avascular necrosis, cardiovascular (congestive heart failure, myocardial infarction, coronary artery disease, deep vein thrombosis), pulmonary (cryptogenic organizing pneumonia, diffuse alveolar hemorrhage, noninfectious interstitial pneumonitis/idiopathic pneumonia, acute respiratory distress syndrome), diabetes mellitus, gonadal dysfunction/infertility necessitating hormone replacement, seizure, stroke, renal failure requiring dialysis, liver toxicity, pancreatitis, thrombotic microangiopathy/hemolytic uremic syndrome, hemorrhagic cystitis, growth hormone deficiency/growth disturbance, neuropathy, cholecystitis/cholelithiasis, hypertension, osteopenia/osteoporosis, and SN. Cataracts and hypothyroidism were excluded from the analysis because they were not considered to have significant long-term clinical consequences relative to other LEs. In addition, the "other" category, which includes chronic obstructive pulmonary disease, pulmonary fibrosis, and other restrictive diseases, also was excluded owing to a low number of events. Individual organ toxicities were grouped into an NM-LE category owing to a low number of events.

Statistical Analysis

The primary objective of this study was to determine the association of cGVHD with first malignant LEs and first NM-LEs among 2-year survivors of childhood HCT. A landmark analysis was conducted at the 2-year post-transplantation date for all patients. Two-year survivors were chosen for this analysis because the majority of patients developed cGVHD by 2-years post-transplantation. Survivors who developed GVHD after the 2-year landmark date were included in the "no cGVHD" cohort. Secondary objectives included determining cGVHD-related factors (maximum grade, maximum severity, onset type, organ involvement, platelet count at diagnosis) and the duration of systemic immunosuppression on the development of first LEs.

Categorical variables were summarized using standard descriptive measures. Chi-square and Wilcoxon statistics were used to compare the distribution of patient, disease, transplant-related and cGVHD-related factors. The prevalence of individual LEs occurring at ≥2 years post-transplantation among 2-year survivors of HCT was computed. Owing to a low number of events, individual LEs were further categorized as SN or nonmalignant. The cumulative incidence probability of any first LE, SN or NM-LE at 3, 5, and 10 years after HCT was estimated while treating death or disease relapse as a competing risk. Gray's test was used to compare cumulative incidence functions between the 2 patient groups.

The association of cGVHD and LEs was assessed using a Cox proportional hazards regression model. Time to development of first LE was the endpoint, and time to cGVHD (occurring before the LE) was treated as a time-dependent variable. All the clinical variables were tested for violation of the proportional hazard assumption. Variables that violated the proportional hazards assumption were adjusted through stratification. A stepwise model building procedure was used to identify patient-, disease-, and HCT-related covariates, with a threshold of .05 for both entry into and retention in the models. Center effect was adjusted for in all models. cGVHD was the main effect for all LE outcomes, and additional variables included in the initial models for any LE and NM-LE were donor/recipient cytomegalovirus serostatus match, disease status prior to HCT, and receipt of total body irradiation (TBI). Body mass index/weight for age percentile and receipt of TBI were included in the model for malignant LEs.

The effects of cGVHD-related factors on the development of first LEs was also analyzed by Cox regression using the same set of covariates from the initial models. To adjust for multiple testing, specific cGVHD variables with $P < .01$ were considered significant. The majority of patients who developed cGVHD had a long follow-up time (90% with >44 months) compared with their time to onset of cGVHD plus the treatment duration of cGVHD (75% with <43 months). Thus, the duration of systemic immunosuppression was treated as a time-dependent variable for the development of first LEs. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

The rate of cancer occurring after 2 years post-transplantation in the study population versus the general population was compared using methods described in previous CIBMTR studies [8,15]. In addition, the standardized incidence ratios between patients with cGVHD and those without cGVHD were compared.

RESULTS

Patient Characteristics

The study population comprised 1260 survivors of HCT performed for a childhood hematologic malignancy. Baseline patient demographics and transplantation characteristics

Table 1
Baseline Characteristics of Patients Receiving First Myeloablative HCT for Childhood Hematologic Malignancy between 2000 and 2010 and Surviving Disease-Free for 2 Years Post-HCT

Variable	cGVHD by 2 Years Post-HCT	
	Yes	No
No. of patients	491	769
Follow-up of survivors, mo, median (range)	119 (24-222)	119 (24-238)
Age at HCT, yr, median (range)	10 (.3-17.96)	8 (.35-17.91)
Male sex, n (%)	289 (59)	455 (59)
Caucasian race, n (%)	406 (83)	664 (86)
Body mass index at HCT, n (%)		
<5th percentile	38 (8)	52 (7)
5th-95th percentile	365 (74)	607 (79)
>95th percentile	88 (18)	110 (14)
Lansky score ≥90, n (%)	679 (88)	437 (89)
Disease, n (%)		
Acute myelogenous leukemia	157 (32)	299 (39)
Acute lymphoblastic leukemia	256 (52)	346 (45)
Chronic myelogenous leukemia	47 (10)	58 (8)
Myelodysplastic syndrome/myeloproliferative neoplasm	31 (6)	66 (9)
Disease status at HCT, n (%)		
Early	221 (45)	389 (51)
Intermediate	230 (47)	316 (41)
Advanced	38 (8)	47 (6)
Missing	2 (0)	17 (2)
Donor type, n (%)		
HLA-identical sibling	71 (14)	217 (28)
Matched (8/8) unrelated	167 (34)	182 (24)
Mismatched (7/8) unrelated	83 (17)	85 (11)
Cord blood	170 (35)	285 (37)
Graft type, n (%)		
Bone marrow	226 (46)	404 (53)
Peripheral blood	95 (19)	80 (10)
Cord blood	170 (35)	285 (37)
MAC TBI*, n (%)		
No	127 (26)	295 (38)
Yes	364 (74)	474 (62)
Donor-recipient sex match, n (%)		
Male-male	161 (33)	258 (34)
Male-female	100 (20)	181 (24)
Female-male	124 (25)	186 (24)
Female-female	101 (21)	127 (17)
Cord blood, male recipient	4 (1)	11 (1)
Cord blood, female recipient	1 (0)	6 (1)
Donor/recipient CMV serostatus, n (%)		
+/+	103 (21)	140 (18)
+/-	64 (13)	92 (12)
-/+	129 (26)	214 (28)
-/-	195 (40)	323 (42)
GVHD prophylaxis, n (%)		
CNI + MTX ± others	289 (59)	434 (56)
CNI + MMF ± others	105 (21)	113 (15)
CNI ± others (excluding PTCy, MMF, and MTX)	66 (130)	172 (22)
Ex vivo TCD/CD34 selection	31 (6)	50 (7)
Year of HCT, n (%)		

(*continued*)

Table 1 (*Continued*)

Variable	cGVHD by 2 Years Post-HCT	
	Yes	No
2000-2003	134 (27)	256 (33)
2004-2007	213 (43)	325 (42)
2008-2010	144 (29)	188 (24)

CNI, calcineurin inhibitor; CMV, cytomegalovirus; MMF, mycophenolate mofetil; MTX, methotrexate; PTCy, post-transplantation cyclophosphamide; MAC, myeloablative conditioning; TCD, T cell depletion.

* TBI dose of 500 cGy (nonfractionated) or > 800 cGy (fractionated).

stratified by having cGVHD versus no cGVHD by 2 years post-HCT are described in Table 1. cGVHD developed by 2 years post-HCT in 491 survivors (39%). The median age at HCT for survivors with cGVHD and no cGVHD was 10 years and 8 years, respectively, and the median duration of follow-up was 119 months (range, 24 to 222 months) and 119 months (range, 24 to 238 months), respectively. Among survivors with cGVHD, 61% had extensive maximum grade. Other characteristics of survivors with cGVHD included mild (54%) or moderate (32%) cGVHD severity, interrupted onset type (47%), platelet count $\geq 100 \times 10^9$/L at cGVHD diagnosis (70%), both mucocutaneous and visceral organ involvement (58%), and duration of systemic immunosuppression >2 years (17%) (Table 2). The median time to the onset of cGVHD was 5.4 months (range, 1 to 23 months). At the time of analysis, 70 (14%) and 46 (6%) deaths occurred in survivors with cGVHD and those without cGVHD, respectively, with relapse of the primary disease as the most common cause of death in both groups (cGVHD: 27%; no cGVHD: 43%) (Supplementary Table S1). However, it is noteworthy that the 10-year cumulative incidence of disease relapse was significantly lower in the cGVHD cohort (9.6% [95% CI, 8.5% to 10.8%] versus 17% [95% CI, 14.9% to 19.3%]) (data not shown), suggesting that cGVHD may be protective against relapse. Death due to cGVHD was the second most common cause of death among survivors with cGVHD and was nearly equal to the rate of death due to primary disease (26%). Excess deaths in the cGVHD group were attributed to cGVHD itself and infection. Ten patients in the no cGVHD group developed cGVHD after the 2-year landmark date, and 3 deaths (7%) occurred due to GVHD itself.

Table 2
cGVHD Characteristics of Patients who Developed cGVHD by 2 Years Post-HCT following First Myeloablative HCT for Childhood Hematologic Malignancy between 2000 and 2010

Characteristic	Value
Time to onset of cGVHD, mo, median (range)	5.39 (1.78-23.13)
Maximum grade of cGVHD, n (%)	
Limited	192 (39)
Extensive	299 (61)
Severity of cGVHD, n (%)	
Mild	264 (54)
Moderate	157 (32)
Severe	70 (14)
Onset type of cGVHD, n (%)	
Progressive	107 (22)
Interrupted	233 (47)
De novo	99 (20)
Missing	52 (11)
Platelet count at cGVHD diagnosis, $\times 10^9$/L, n (%)	
≥100	345 (70)
<100	108 (22)
Missing	38 (8)
cGVHD organ involvement, n (%)	
Mucocutaneous	169 (34)
Visceral	35 (7)
Both	287 (58)
Duration of systemic immunosuppression, n (%)	
≤6 mo	70 (14)
6-12 mo	69 (14)
1-2 yr	75 (15)
>2 yr	85 (17)
Not treated	10 (2)
Missing or dead/relapsed	182 (37)

SNs and NM-LEs

The frequencies of individual SNs and NM-LEs occurring ≥2 years after HCT in patients with GVHD and those without cGVHD are shown in Table 3. SNs at ≥2 years post-HCT occurred at a similar frequency in the 2 groups: 24 (9%) in the cGVHD group and 26 (9%) in the no cGVHD group. Except for a significantly higher frequency of renal dysfunction in the cGVHD group (4% versus 1%; $P < .01$), the frequency of NM-LEs was also similar in the 2 groups.

Any first LE occurring ≥2 years after HCT was reported in 186 (38%) evaluable patients with cGVHD and in 206 (28%) evaluable patients without cGVHD. A first SN occurred in 21 patients from each group (4% in the cGVHD group; 3% in the no cGVHD group) (Supplementary Table S3). Basal cell/squamous cell skin cancers and thyroid cancers occurred more frequently in survivors with cGVHD, whereas more patients without cGVHD developed secondary central nervous system malignancies. An NM-LE occurred in 175 (36%) patients with cGVHD and in 197 (26%) without cGVHD. The median time from HCT to any first LE, SN, or NM-LE was similar in the 2 groups (Supplementary Table S4).

Table 3
Prevalence of LEs at ≥2 Years after HCT in 2-Year Disease-Free Pediatric Survivors with and without cGVHD by 2 Years Post-HCT

LE	cGVHD by 2 Yr Post-HCT, n (%)		*P* Value*
	Yes	No	
Avascular necrosis	19 (7)	11 (4)	.09
Pulmonary†	11 (4)	13 (5)	1
Cardiovascular	3 (1)	9 (3)	.15
Diabetes	9 (4)	10 (4)	1
Gonadal dysfunction	63 (25)	98 (35)	.01
Stroke, seizure	5 (2)	1 (0)	.11
Renal dysfunction	11 (4)	2 (1)	**<.01**
Liver toxicity, pancreatitis	13 (5)	11 (4)	.53
New malignancy	24 (9)	26 (9)	1
TTP, HUS	3 (10)	0 (0)	.10
Hemorrhagic cystitis	0 (0)	1 (0)	1
Growth disturbance	82 (32)	94 (33)	.85
Neuropathy	0 (0)	2 (1)	.50
Cholecystitis, cholelithiasis	2 (1)	1 (0)	.60
Hypertension	1 (0)	2 (1)	1
Osteoporosis, osteopenia	8 (3)	3 (1)	.13

HUS indicates hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

* Fisher exact test.

† Cryptogenic organizing pneumonia, interstitial pneumonitis, acute respiratory distress syndrome, pulmonary hemorrhage, other pulmonary abnormality, myocardial infarction, congestive heart failure, coronary artery disease, and deep vein thrombosis.

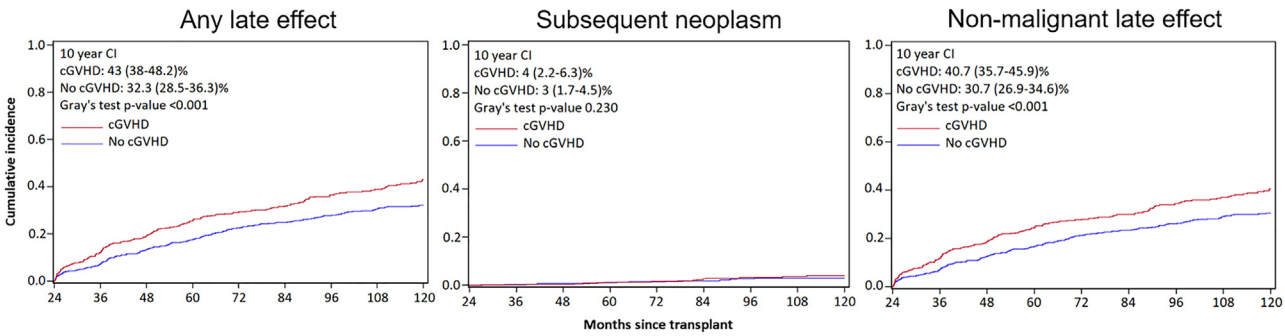

Figure 1. Cumulative incidence of first LE at 10 years.

The estimated 10-year cumulative incidence of any LE (43% versus 32%; $P < .001$) and of any NM-LE (41% versus 31%; $P < .001$) was significantly different in the 2 groups (Figure 1, Supplementary Table S5). There was no significant between-group difference in the cumulative incidence of SNs over time (4% versus 3%; $P = .23$).

Association of cGVHD with SNs and NM-LEs

Multivariate analysis of predictors demonstrated that having cGVHD was associated with any LE (HR, 1.38; 95% CI, 1.13 to 1.68; $P = .001$) and NM-LE (HR, 1.37; 95% CI, 1.10 to 1.70; $P = .006$), but not SN (HR, 1.30; 95% CI, .73 to 2.31; $P = .38$) (Figure 2, Supplementary Table S6). TBI, on the other hand, was significantly associated with the development of SN (HR, 16.59; 95% CI, 2.21 to 124.25; $P = .006$) and NM-LEs (HR, 1.80; 95% CI, 1.39 to 2.33; $P < .0001$). A subset analysis of patients who received TBI showed no statistically significant difference in the risk of SN among patients who developed cGVHD and those without cGVHD. However, a significant association between cGVHD and NM-LE was observed among those exposed to TBI (HR, 1.37; 95% CI, 1.09 to 1.73; $P = .007$) but was not seen in the TBI-nonexposed group (HR, 1.55; 95% CI, .97 to 2.49; $P = .07$). A test for interaction was not significant.

Further multivariate analysis of cGVHD-related factors showed that cGVHD with extensive grade (HR, 1.60; 95% CI, 1.23 to 2.08; $P = .0005$), severe cGVHD (HR, 2.25, 95% CI, 1.60 to 3.17; $P < .0001$), interrupted onset type (HR, 1.57; 95% CI, 1.21 to 2.05; $P = .0008$), and both mucocutaneous and visceral organ involvement (HR, 1.59; 95% CI, 1.24 to 2.03; $P = .0002$) were independently associated with the development of an NM-LE. NM-LEs were seen more frequently in patients with moderately severe cGVHD (HR, 1.40; 95% CI, 1.01 to 1.93; $P = .042$) and progressive onset type (HR, 1.44; 95% CI, 1.00 to 2.06; $P = .048$), but these associations did not reach statistical significance (Figure 3). The duration of treatment with systemic immunosuppression was not significantly associated with an increased risk of NM-LEs.

Finally, multivariable analysis did not demonstrate a significant association between any cGVHD-related factors, including duration of treatment with systemic immunosuppression, with SNs.

DISCUSSION

We report results from the first systematic analysis of the association of cGVHD and LEs occurring in ≥2-year survivors of pediatric HCT performed for hematologic malignancy. In this cohort, we found that cGVHD is independently associated with the development of NM-LEs but not with SNs at ≥2 years following HCT. We also report that cGVHD-related features representing a more severe state of systemic immune dysfunction or inflammation are associated with a greater occurrence of late organ toxicities. These findings are clinically important,

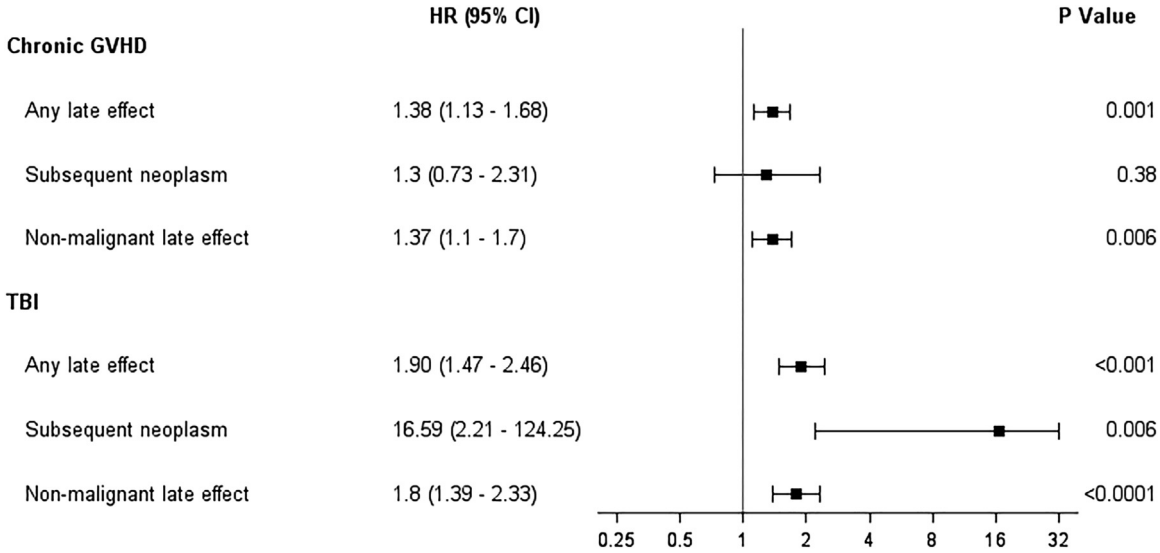

Figure 2. Impact of cGVHD on first SN and NM-LE.

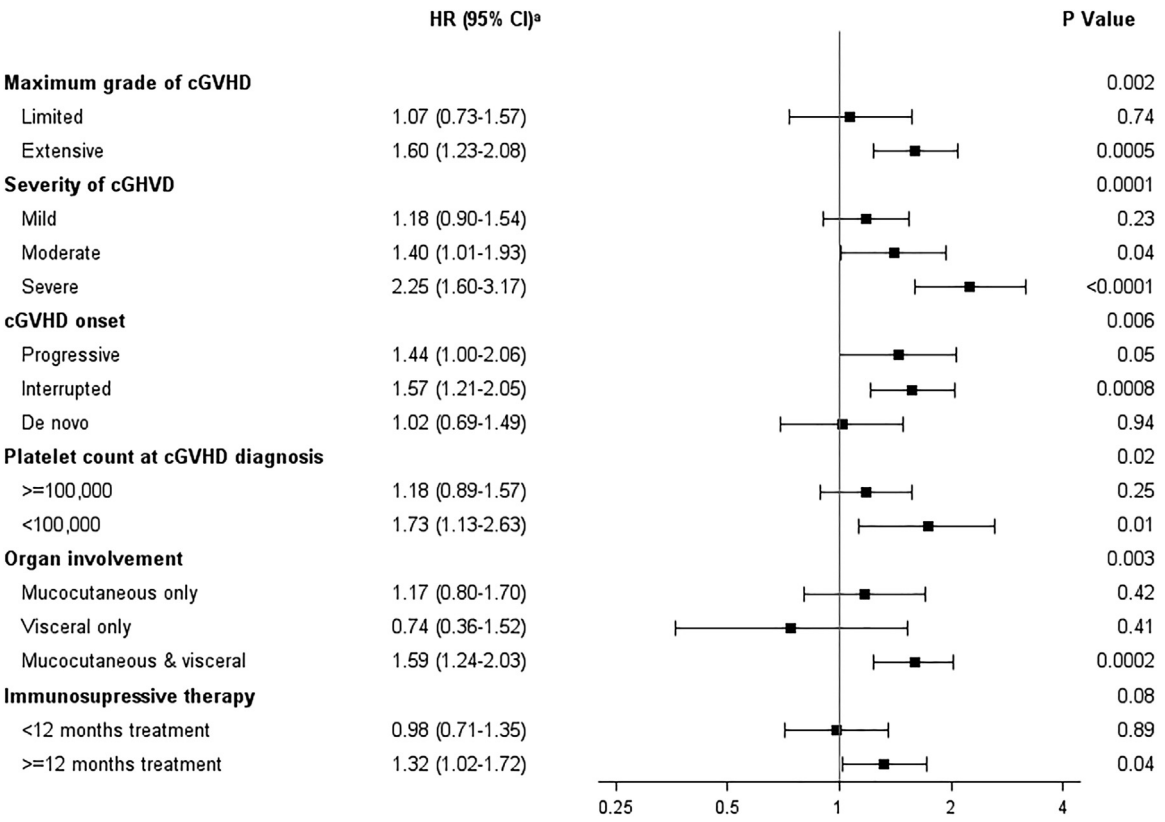

Figure 3. Impact of cGVHD-related factors on first NM-LE. [a]Reference value, 1.00 (no cGVHD).

given that data regarding differences in the epidemiology of LEs among children with cGVHD and those without cGVHD could modify current guidelines for the screening and prevention of malignant LEs and NM-LEs following transplantation.

The incidence of cGVHD at 2 years post-HCT in our study was 39%, which is somewhat higher than that in previously published reports [9,10]. This difference might be related to differences in reporting of cGVHD across transplantation centers; however, this finding did not translate to improved relapse rate or disease-free survival in unadjusted survival analyses (data not shown). We found no significant association between the estimated cumulative incidence of SNs and cGVHD. This result is surprising, given that several reports have described cGVHD as a risk factor for secondary malignant neoplasms in children, including cancers of the skin [16,17] and thyroid [18]. Although our findings may be limited by the relatively small number of SN events in out cohort (n = 42), our results are consistent with previous studies showing no adverse effect of cGVHD on the development of secondary solid tumors in long-term survivors of HCT for childhood leukemia [19] or of SNs among adolescent and young adult HCT survivors [8]. Unlike the adolescent and young adult study in which the median follow-up among the population was 6.4 years [8], the median follow-up of patients with cGVHD and those without cGVHD in our analysis was 9.9 years. It is possible that the latency period for the development of clinical SNs occurs over decades and that both studies might not have had adequate follow-up to capture SNs. In a recent report focused on the development of SNs in children and adult survivors of myeloablative and reduced-intensity conditioning HCT performed at the Fred Hutchinson Cancer Research Center [20], cGVHD was the strongest risk factor for squamous cell cancers in nonskin sites but not for other SNs. However, whether this association would have persisted had the children been studied separately from adults in this analysis is unclear. In our study, all HCT recipients had a significantly higher risk of SNs compared with the general population (27-fold higher in patients with cGVHD and 19-fold higher in those without cGVHD), but the increased risk was comparable in the 2 groups. We also found that the median time to development of a first SN did not differ between the 2 groups. Exposure to TBI, on the other hand, appeared to be associated with the greatest risk for the development of SNs in this cohort of children. This is consistent with the Fred Hutchinson Cancer Research Center study showing that conditioning regimens consisting of a TBI dose of >450 cGy were predictive of SN [20]. Finally, we found no significant association between prolonged use of systemic immunosuppression for cGVHD and SNs. The postulation that prolonged treatment with immunosuppressive therapies may impair tissue repair in an environment of chronic inflammation and tissue damage, leading to enhanced risk for tumor development [16] was not supported here; however, this finding may be related to the low number of SNs in this cohort. Although our findings do not suggest that cGVHD differentially affects the incidence OF or time of onset to SNs in the first decade post-HCT, it does underscore the importance of education about malignant LEs and life-long surveillance of SNs (including skin and oral cancers) for all survivors of pediatric HCT.

The cumulative incidence of NM-LEs was higher in our patients with cGVHD. Although we were unable to perform detailed analyses of several clinically relevant organ impairments, such as cardiovascular diseases and bone disorders, because of a low number of events, we did find a significantly higher frequency of renal dysfunction in the patients with cGVHD. Presumably, this finding could be related to use of

calcineurin inhibitors to treat cGVHD or due to cGVHD itself. On the other hand, gonadal dysfunction was less prevalent in the cGVHD group, for unclear reasons. We found a disturbing rate of occurrence for all NM-LEs over a 10-year period in the patients without cGVHD, and even more so in patients with cGVHD (Supplementary Table S5). The cumulative incidence did not appear to plateau by 10 years post-HCT in either group, and this finding may warrant patient counseling about the continued risk of developing NM-LEs beyond the first decade post-transplantation.

We identified cGVHD as an independent risk factor for these nonmalignant disorders, confirming previous studies linking cGVHD to a multitude of chronic health conditions [8,21,22]. On the other hand, we did not observe any difference in the median time of onset of a first NM-LE between patients with cGVHD and those without cGVHD. TBI also was found to independently increase the risk of NM-LEs, and we found a significant association between cGVHD and NM-LEs among those exposed to TBI. Our analysis found no statistical interaction between cGVHD and TBI, and the lack of a significant association between cGVHD and NM-LEs in the non-TBI-exposed group might have been related to a smaller sample size and lack of power.

Importantly, we identified features of cGVHD that indicate a more intensive state of immune dysregulation to confer a major risk to late toxicities in this young cohort. cGVHD of extensive grade and severe cGVHD were associated with an up to >2-fold greater risk of an NM-LE compared with no cGVHD. This finding aligns with our observation that cGVHD involving both mucocutaneous and visceral organs, and not mucocutaneous or visceral involvement alone, was a risk factor for the development of NM-LEs. Patients with a prior history of aGVHD (progressive or interrupted onset type) appeared to be at greater risk of this outcome than those without aGVHD, likely because of the longer exposure of tissue to inflammation and autoimmunity and possibly to longer duration of treatment with systemic immunosuppression for both aGVHD and cGVHD.

In our model, we did not find a significant association between the risk for an NM-LE and the duration of systemic immunosuppressive drug use. Although we were not able to ascertain the specific drugs given for cGVHD and each duration of treatment via the reporting method used for collection of this dataset, it is safe to assume that corticosteroids were the primary agents or the backbone of treatments used in this cohort. The long-term toxicities of systemic corticosteroids on multiple organ systems are well known, and one possible explanation for the finding is that children who received prolonged corticosteroid treatment did not survive to 2 years after transplantation and were not included in this cohort. As newer therapeutics with potentially higher efficacy and longer duration of response become available for steroid-refractory cGVHD [23,24], patients may have a better chance of avoiding long exposure to corticosteroid toxicity. Overall, our findings underscore the importance of refining HCT conditioning regimens that result in cure without incurring GVHD and of developing better strategies to prevent and treat cGVHD with effective steroid-sparing regimens.

We acknowledge several limitations of the present study. Ascertainment bias, inherent in many retrospective studies, was present. Although the follow-up of our patients is nearly complete at 5 years after HCT, the 10-year completion rate of follow-up was <90%. We also had missing data in our dataset, as exemplified by 36% of patients without data on the duration of cGVHD treatment. We are reassured that the 10-year cumulative incidence of subsequent malignant neoplasms in our analysis is similar to that in previous reports [8,20]; however, we cannot be certain that all SNs were reported to the CIBMTR, thereby affecting our interpretations. Furthermore, it is well reported that SNs and some other NM-LEs, such as those of cardiac origin, can appear decades after HCT [25–27]. Although we set our patient inclusion criteria to allow a minimum of a 10-year follow-up period, it is possible that a longer follow-up is needed to capture these clinically significant complications of HCT.

Similarly, the relatively low number of individual medical LEs reported to the CIBMTR hampered our ability to compare the incidence and effect of cGVHD on these individual toxicities. We also were unable to capture important psychological complications in our young survivors due to reporting methods and limited use of patient-reported outcomes during the years included in this study. We did not have access to pre- or post-HCT information on other exposures, including previous anticancer treatments, family medical history, tobacco and alcohol use, and UV sunlight exposure, which may modify the risk for SNs or cardiac diseases. Finally, we did not evaluate the effects of aGVHD and treatments for this complication in our models.

While acknowledging the challenges inherent in all retrospective studies of LEs, we believe that our study provides novel information on the impact of certain cGVHD characteristics on LEs in survivors of childhood HCT. Patients with milder features of cGVHD have a similar risk of SNs and NM-LEs as patients without cGVHD, and those with more severe cGVHD manifestations warrant enhanced vigilance for all LEs. New recommendations for LE surveillance and management stratified by the presence of cGVHD cannot be made based on our findings, and the current LE surveillance guidelines provided by the Children's Oncology Group, which addresses these high-risk groups, should remain a primary resource for providers who care for these patients [1,28]. Furthermore, pediatric and adult survivorship clinics that focus on the long-term care of survivors of childhood HCT, including adolescents and young adults who transition to adult care, remain an important central resource to ensure that our young survivors are reaching their full life potential [29,30]. Future research should continue this work and reevaluate the impact of cGVHD on LEs using the 2014 National Institutes of Health consensus criteria for cGVHD [31]. Other areas of investigation include assessing the impact of new prophylactic and therapeutic options for cGVHD on late organ toxicities and interactions among pre-HCT therapies, lifestyle behaviors, genetic predisposition, and cGVHD on the development of LEs.

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SUPPLEMENTARY MATERIALS

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