Visual, Auditory, Sensory, and Motor Impairments in Long-Term Survivors of Hematopoietic Stem Cell Transplantation Performed in Childhood

Results from the Bone Marrow Transplant Survivor Study

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BACKGROUND. Because of treatment-related toxicity, research is increasingly being focused on long-term sequelae secondary to hematopoietic stem cell transplantation (HSCT) in survivor populations.

METHODS. This study describes the incidence of auditory, sensory, motor, and visual impairments, including cataracts, among 235 individuals who were treated with HSCT during childhood or adolescence. Outcomes were compared with 705 siblings of childhood cancer survivors. Participants completed a survey with questions on posttransplant organ system impairments. Approximately half of survivors were transplanted when younger than 10 years of age. The median length of followup was 11 years.

RESULTS. The cumulative incidence of cataracts was 36% at 15 years post-HSCT, although cataracts occurred only in those who received total body irradiation as an HSCT conditioning agent or head irradiation before transplant. Persistent pain was reported by 21% of survivors. Loss of hearing in one or both ears, and legal blindness in one or both eyes, each occurred after transplant in 2% of survivors. Occurrences were uncommon, but survivors were 4.3 times (95% confidence interval [CI]: 2.0–9.4) more likely to report coordination problems, 7.7 times (95% CI: 3.2–18.5) more likely to report chewing or swallowing problems, and 3.5 times (3.5; 95% CI: 1.6–7.9) more likely to report muscle weakness than those in the comparison group. Muscle weakness was strongly associated with positive history of chronic graft-versus-host disease.

CONCLUSIONS. Increased risks were found for motor impairments, hearing loss, vision loss, and persistent pain among study participants. Cataracts were a frequent adverse effect, suggesting that close monitoring with appropriate intervention for preservation of vision, particularly among those who received total body irradiation, should be a primary goal in survivors of HSCT performed in childhood.
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Combined data from the International Bone Marrow Registry and the Autologous Bone and Marrow Transplant Registry show that approximately 50,000 hematopoietic stem cell transplantations (HSCTs), including 5,400 recipients age 20 years or younger, are performed worldwide each year.[1,2] A variety of life-threatening childhood conditions are now successfully treated with HSCT, as either a first-line or rescue therapy. Improved survival rates have sharpened the need for research that is focused on adverse medical effects that may emerge or persist many years after treatment.[2,3] Long-term con-

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sequences, both medical and psychosocial, may result from the underlying disease process, the treatments used, the acute toxicity and sequelae from treatment, and from associated conditions that emerge long after treatment and cure. With HSCT for malignancies and hematologic disorders, where ablative chemotherapy and often total body irradiation (TBI) are used as conditioning modalities in preparation for infusion of progenitor cells, the opportunity for late adverse effects is particularly evident.[4–6]

Patients who receive HSCT from an allogeneic source are also at risk for the development of acute (within 100 days of transplant) and chronic (after 100 days) graft-versus-host disease (GVHD) in which antigenic disparities between the donor T-lymphocytes and recipient cells result in tissue injury, often severe, involving the skin, and/or liver, and/or gastrointestinal tract.[4,7] Cyclosporine A is a drug commonly used to treat chronic GVHD. Neurotoxicity is a recognized complication of cyclosporine A, and may include generalized seizures, occipital blindness, and hemiparesis. Magnetic resonance imaging (MRI) findings in allogeneic recipients indicate hyperintensity lesions, predominantly in the posterior cerebrum, with both subcortical and cortical involvement, and cerebellar lesions, suggesting vascular injury as a contributing factor in the pathology of neurotoxicity.[8] In another study of adult recipients of allogeneic transplantation,[9] the occurrence of microangiopathy after transplantation, observed in seven of eight patients with chronic GVHD evolving from acute GVHD, had an unfavorable influence on neurologic status. Cyclosporine treatment of longer than 6 months was also associated with increased risk for neurologic sequelae in that study.[9]

Most reports on long-term consequences of HSCT have focused on transplants performed in adults, or have incorporated results on children in a largely adult cohort of survivors. Some of the consequences reported after HSCT performed in childhood include subsequent malignancies[10–12]; pulmonary compromise[13–15]; endocrine dysfunction, including hypothyroidism, gonadal failure, infertility, and growth attenuation[16–19]; and functional limitations.[20] Very few studies have included evaluations of neurologic functioning in long-term survivors of HSCT performed in childhood. This analysis from the Bone Marrow Transplant Survivor Study (BMTSS) describes the incidence of cataracts and of neuromotor and neurosensory outcomes among 235 individuals who were treated with HSCT during childhood or adolescence, and compares outcomes to 705 siblings of childhood cancer survivors.

MATERIALS AND METHODS

Subjects

The BMTSS is a collaborative study between City of Hope Cancer Center and the University of Minnesota. The study was established in 2000 to evaluate health outcomes in a cohort of children and adults diagnosed with cancer or other life-threatening illnesses treated with HSCT. Eligibility criteria for this analysis included receiving HSCT between January 1, 1974, and December 31, 1998, at age 20 years or younger; surviving at least 2 years after transplant and alive at interview date; and ability to provide informed consent and complete a questionnaire in English. The comparison group for this analysis is composed of a sample of siblings from a cohort of childhood cancer survivors[21] who completed a questionnaire between 1996 and 2003 containing the same questions as those used in this study. To form a near identical distribution of demographic characteristics, comparison group participants were frequency-matched to cases at a ratio of 3:1 and randomly selected from 3,845 eligible members from within six age groups ($<$ 10 yrs, 11–14 yrs, 15–17 yrs, 18–29 yrs, 30–39 yrs, 40 yrs or older), two sex groups, and two broad race/ethnicity categories (white, nonwhite). The percentage of parent respondents was 33% for both the survivors and the comparison group. The informed consent process and the study protocols and documents were approved by the Human Subjects Research Review Committees at the two collaborating institutions.

Data Collection

Participants completed the BMTSS questionnaire, a survey with questions on organ system impairments including when the problem was first diagnosed by a physician or other healthcare provider. Questions were also asked on prevalent medical conditions, medication use, health status, health behaviors, pregnancy history, demographic characteristics, socioeconomic indicators, and insurance coverage. The BMTSS questionnaire is identical to the survey developed for use in the 14,000-subject Childhood Cancer Survivor Study,[22] with a few additional questions specifically related to HSCT. The self-report BMTSS questionnaire was evaluated for reliability on a random sample of 100 HSCT survivors. The agreement with medical records was excellent (kappa $>$ 0.8) for musculoskeletal, cardiovascular, pulmonary, and endocrine impairments. Agreement was moderate (kappa 0.4–0.7) for second cancers, central nervous system disorders, and eye problems.[23]

Outcome Variables

Four general categories of neurologic impairments were considered: auditory, visual, motor, and sensory. Auditory impairments included the following medical conditions: any hearing loss (hearing loss requiring a hearing aid, or partial or complete deafness in one or both ears), tinnitus, and persistent dizziness or vertigo. Visual impairments included legal blindness in one or both eyes, cataracts, and double vision. Motor impairments included coordination difficulties (problems with balance, equilibrium or manipulation skills, and tremors or movement disorder), problems chewing or swallowing, and muscle weakness. Sensory deficits included a decreased or abnormal sense of touch or feeling in hand, fingers, arms or legs, an abnormal sense of taste or smell, and persistent pain.

Independent Variables

Transplant type (autologous or allogeneic), conditioning regimen (with or without TBI), and, among allogeneic recipients, past or present chronic GVHD (yes or no) were considered as potential risk factors for these analyses. Time since transplant, age at interview, race/ethnicity, and sex were considered as possible modifiers or confounders. Information on transplant type, treatment, and GVHD was obtained from the HSCT databases at each institution.

Data Analysis

The incidences of visual, auditory, sensory, and motor impairments were identified by tabulating affirmative responses to the associated questions presented in the BMTSS questionnaire, but only if the participant reported that the complication first occurred after the transplant date. Two sample *t*-tests for continuous variables, and chi-square tests for dichotomous variables, were used to compare differences between survivors and the sibling comparison group, and between allogeneic recipients with or without chronic GVHD, by sex, race, transplant institution, and age at interview.

The incidence of each medical late effect was compared between survivors and the comparison group by calculating risk ratio (RR) and 95% confidence intervals (95% CI) using generalized estimating equations (GEE) with a Poisson distribution and a log link.[24,25] The factors used to select cases for frequency matching, i.e., age group, sex, and race/ethnicity, were evaluated as independent predictors of the outcomes, and as possible confounders in the models. Reflecting the successful frequency matching scheme, the matching variables did not appreciably alter the risk estimates, so they were not included as covariates in the final models that compared incidence of impairments between survivors and siblings of cancer survivors.

In an analysis limited to allogeneic recipients only, chronic GVHD status was evaluated in relation to the outcome variables using generalized estimating equations. These models were adjusted for age at transplant, time since transplant, and sex. Race/ethnicity did not appreciably alter the estimates and was not included in the reporting of results. Potential confounding by age at transplant, sex, time since transplant, and chronic GVHD was examined by looking at the strength and the precision of risk estimates in both full and reduced models.

Cumulative incidence of cataracts, overall, by chronic GVHD history, and by whether or not TBI was used as a conditioning treatment, was calculated in a competing risk analysis using the Markov Chain Approach of Aalen and Johansen.[26,27] Wilcoxon signed rank tests were used to compare cumulative incidence rates by transplant type among survivors and by chronic GVHD history among allogeneic recipients. SAS v. 9.1 was used for all analyses (SAS Institute, Cary, NC).

RESULTS

Recruitment

A total of 528 potentially eligible patients were identified at the two institutions. Of these, eligibility could not be confirmed for 136 patients (25.7%) who were lost to followup and could not be contacted. An additional 131 (24.8%) declined participation, and 26 (4.9%) had yet to complete the study questionnaire and are considered passive refusals. The questionnaire was completed by 235 participants (157 survivors and 78 parents of survivors), representing 45% of those initially identified and 60% of those successfully contacted. Participants were more likely than potentially eligible nonparticipants to be female (44% vs. 34%, $P = 0.02$), but did not differ statistically by race ($P = 0.06$), treatment institution ($P = 0.55$), age at transplant ($P = 0.42$), transplant type ($P = 0.81$), HSCT conditioning regimen ($P = 0.19$), or by history of chronic GVHD ($P = 0.27$). From the 3:1 frequency matching strategy, data from 705 childhood cancer siblings were included as the comparison group for this analysis.

Participant Characteristics

The median age at survey completion was 21 years for both the HSCT survivors (range, 5–42 years) and the comparison group (range, 5–50 years). Table 1 provides characteristics of the study participants. The most common cancer diagnoses were acute myeloid

TABLE 1
Characteristics of Study Participants and the Comparison Group

	Survivors (*N* = 235)		Comparison Group (*N* = 705)	
	n	(%)	*n*	(%)
Gender				
Male	131	(55.7)	393	(55.7)
Female	104	(44.2)	312	(44.2)
Race/ethnicity				
White	199	(84.7)	597	(84.7)
Hispanic	18	(7.7)	53	(7.5)
Other	18	(7.7)	55	(7.8)
Treating institution				
City of Hope	58	(24.2)	NA	
University of Minnesota	177	(75.7)	NA	
Age at interview				
< 18 yrs	78	(33.2)	234	(33.2)
18 + yrs	157	(66.8)	471	(66.8)
Age at transplant				
< 5 yrs	61	(25.9)	NA	
5–9 yrs	57	(24.2)	NA	
10+ yrs	117	(49.8)	NA	
Time since transplant				
2–5 yrs	43	(18.3)	NA	
6–10 yrs	81	(34.5)	NA	
11+ yrs	111	(47.2)	NA	
Primary diagnosis				
Acute lymphoblastic leukemia	62	(26.4)	NA	
Acute myeloid leukemia	70	(29.8)	NA	
Aplastic anemia	31	(13.2)	NA	
β-Thalassemia major	1	(0.4)	NA	
Chronic myeloid leukemia	15	(6.4)	NA	
Ewing sarcoma	5	(2.1)	NA	
Fanconi anemia	7	(3.0)	NA	
Hodgkin disease	9	(3.8)	NA	
Myelodysplastic syndrome	9	(3.8)	NA	
Neuroblastoma	16	(6.8)	NA	
Non-Hodgkin lymphoma	7	(3.0)	NA	
PNET or Medulloblastoma	2	(0.8)	NA	
Wilms tumor	1	(0.4)	NA	
Transplant type				
Autologous	58	(24.7)	NA	
Allogeneic	177	(75.3)	NA	
Conditioning regimen				
Chemotherapy	59	(25.1)	NA	
Total body irradiation and chemotherapy	176	(74.9)	NA	

NA: not applicable.

leukemia (30%) and acute lymphoblastic leukemia (26%), and the most common conditioning regimen was a combination of TBI with chemotherapy (75%). Approximately half of the survivors were transplanted when younger than 10 years of age. The median length of followup was 11 years (range, 2–28 years) and 82% had survived at least 6 years since their transplant when interviewed.

TABLE 2
Auditory, Visual, Motor, and Sensory Impairments among Childhood HSCT Survivors and the Comparison Group

	Survivors (*N* = 235)		Comparison Group (*N* = 705)				
	n	(%)	*n*	(%)	RR	(95% CI)	*P*
Auditory impairments							
Hearing loss in one or both ears	6	(2.6)	4	(0.6)	4.5	(1.3–15.9)	0.02
Tinnitus	9	(3.8)	16	(2.3)	1.7	(0.7–3.8)	0.21
Persistent dizziness	8	(3.4)	6	(0.8)	4.0	(1.4–11.5)	0.01
Visual impairments							
Blind in one or both eyes	5	(2.1)	5	(0.7)	3.0	(0.9–10.4)	0.08
Cataract	90	(38.3)	1	(0.1)	270	(38–1937)	< 0.001
Double vision	2	(0.9)	3	(0.4)	2.0	(0.3–12.0)	0.45
Motor impairments							
Coordination problem	16	(6.8)	11	(1.6)	4.3	(2.0–9.4)	< 0.001
Swallowing problem	18	(7.7)	7	(1.0)	7.7	(3.2–18.5)	< 0.001
Muscle weakness	13	(5.5)	11	(1.6)	3.5	(1.6–7.9)	0.002
Sensory impairments							
Abnormal sense of touch	11	(4.7)	13	(1.8)	2.5	(1.1–5.7)	0.02
Persistent pain	49	(20.9)	69	(9.8)	2.1	(1.5–3.1)	< 0.001
Abnormal sense of taste or smell	10	(4.2)	2	(0.3)	15.0	(3.3–68.4)	< 0.001

RR, risk ratios with 95% confidence intervals. HSCT, hematopoietic stem cell transplantation.

Outcome Measures

Hearing loss in one or both ears was reported by 2.6% of survivors (RR: 4.5; 95% CI: 1.3–15.9), and persistent dizziness was reported by 3.4% (RR: 4.0; 95% CI: 1.4–11.5), versus 0.6% and 0.8%, respectively, in the comparison group (Table 2).

Legal blindness in at least one eye was reported by 2.1% of survivors versus 0.7% of the comparison group (RR: 3.0; 95% CI: 0.9–10.4). Occurrence of a cataract was reported by 38% of HSCT survivors, compared with 0.1% of the comparison group (RR: 270; 95% CI: 38–1937; Table 2). Among the 90 survivors with a cataract, 86 (96%) had received TBI as part of their conditioning regimen and 77 (86%) received an allogeneic transplant. The four patients with a cataract who were not exposed to conditioning TBI had been treated with radiotherapy to the head/neck region before HSCT. The cumulative incidence of cataracts, as shown in Figure 1, was 21% at 5 years posttransplant, 32% at 10 years, and 36% at 15 years after HSCT. Survivors of allogeneic HSCT were more likely to report a cataract (cumulative incidence of 40% at 15 years), when compared with survivors of autologous HSCT (cumulative incidence of 21% at 15 years, $P = 0.009$). Furthermore, among survivors of allogeneic HSCT, those with chronic GVHD were more likely to report a cataract (cumulative incidence of 46% at 15

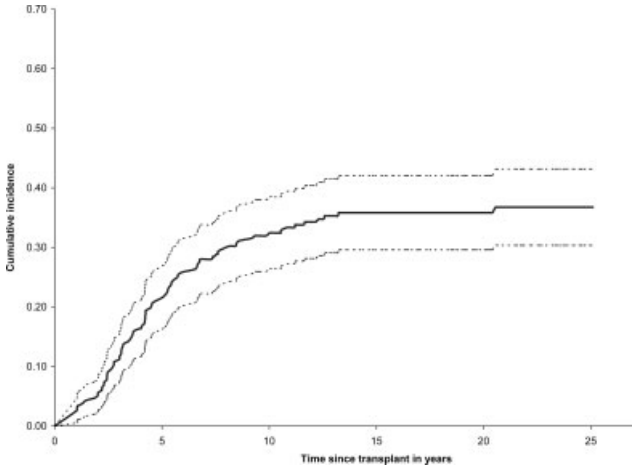

FIGURE 1. Cumulative incidence of cataracts with 95% confidence bounds among childhood HSCT survivors.

years) than were those without a history of chronic GVHD (cumulative incidence of 38% at 15 years, $P = 0.03$). When the analysis was limited to the 176 survivors who received conditioning TBI, however, no differences in cataract incidence was observed by transplant type ($P = 0.47$) or by chronic GVHD history ($P = 0.43$).

Motor impairments represented the highest incidence of reported outcomes among survivors, except for cataracts, ranging from 7.7% for swallowing problems to 5.5% for muscle weakness (Table 2). Survivors were 4.3 times (95% CI: 2.0–9.4) more likely to report coordination problems and 7.7 times (95% CI: 3.2–18.5) more likely to report chewing or swallowing problems than were members of the comparison group. Muscle weakness was also considerably more common among survivors than in the comparison group (RR: 3.5; 95% CI: 1.6–7.9).

Persistent pain was the most common sensory impairment among both HSCT survivors (20.9%) and the comparison group (9.8%, RR: 2.1; 95% CI: 1.5–3.1). Survivors were 2.5 times (95% CI 1.1–5.7) more likely to report an abnormal sense of touch and 15.0 times (95% CI: 3.3–68.4) more likely to report an abnormal sense of taste or smell than was the comparison group (Table 2).

Outcomes and Chronic GVDH

Among the allogeneic transplant recipients, there were no discernable differences in the proportions with a history of chronic GVHD who reported auditory, visual, or sensory impairments when compared with those without a history of chronic GVHD (data not shown). A strong association was observed, however, with muscle weakness, as reported by 19.6% of allogeneic recipients with a history of chronic GVHD history versus 2.3% of those without a history of chronic GVHD (RR: 10.6; 95% CI: 2.5–45.8).

DISCUSSION

With the exception of cataracts and persistent pain, our followup study of persons treated with HSCT as children or adolescents found a relatively low incidence of reported impairments to auditory, visual, motor, and sensory systems. This is encouraging for the increasing number of children who undergo and survive stem cell transplantation for life-threatening disorders. Loss of hearing in one or both ears, and legal blindness in one or both eyes, each occurred after transplant in 2% of the survivors in our study. These outcomes can have a very significant impact on an individual's life, so the 3–4-fold elevated risks for hearing or vision loss, albeit low in actual frequency of occurrence, should be considered when discussing with patients and parents the need for posttherapy surveillance and screening of potential long-term sequelae. Retinal complications after bone marrow transplantation, likely from multifactorial causes, have been described previously and warrant careful long-term monitoring.[28,29] Consistent with our study results, deterioration in hearing after pediatric HSCT was recently reported in a clinical study of 45 children.[30] Platinum compounds used in some chemotherapeutic regimens, particularly cisplatin, are well-established ototoxic agents[31,32] and may be etiologically related to the hearing loss we observed in our study. Motor impairments, notably problems chewing and swallowing, muscle weakness, and coordination problems were reported by 5–8% of our study population. Unfortunately, we were not able to evaluate the severity of these problems or the associated impact on the quality of life and functional abilities of the survivors with these impairments. These findings provide justification for several areas of further research by directed clinical study to better elucidate severity and functional impact of these long-term sequelae.

Also important is the report of persistent pain by 21% of survivors, a twofold (95% CI 1.5–3.1) increased risk over that of the comparison group. Because pain may be an early indicator of disease recurrence or a new malignancy in these patients, and effective treatment options for idiopathic chronic pain are available, pain evaluations are warranted in transplant followup settings and, longer-term, in primary care settings.

The high frequency of cataract occurrence among those who receive TBI as an ablative treatment preceding stem cell infusion is important to note for planning of followup care. Although steroids are

known cataractogenic agents,[33] and often incorporated into treatment of hematologic malignancies and chronic GVHD,[7] we did not find any cases of cataract among study patients who were not treated with TBI or head radiation pre-HSCT. In a followup series of 197 HSCT patients (median age, 25 years), Tichelli et al.[34] found results similar to ours, in that chronic GVHD did not influence the rate of cataract occurrence, a high rate of cataracts was observed among those who received TBI, and only 1 of 33 patients who received chemotherapy without TBI developed a cataract. A recent retrospective analysis of 188 children who received HSCT found that eye shielding during TBI conditioning increased the latency time of cataract formation and decreased the severity of cataracts without increasing risk for central nervous system (CNS)-related recurrence,[35] thus illustrating an approach that could be considered for reducing cataract risk.

The results of this study should be interpreted with an appreciation for certain limitations of this observational study design. First, if participants differed from that of eligible nonparticipants in ways important to our outcome measures, then our frequencies and risk estimates may be biased. Our comparison of treatment-related factors between participants and nonparticipants suggests that there are no obvious problems with our study population, but we cannot rule out the possibility. Second, our outcome measures are based on self-report, from the patient or his or her parent, and we did not confirm the provided information in a clinical setting. Our previous evaluation of these methods in HSCT survivors showed reasonably reliable agreement between medical records and self-reported impairments[23]; however, misclassification of outcome with self-report is certainly a possibility. It should also be noted that, despite our inquiries about date of onset, we could not definitively establish whether the impairments reported in this study, including hearing loss, vision loss, and persistent pain, can be attributed to damage from the underlying disease, any therapies before HSCT, or the HSCT treatment course.

In summary, with the exception of cataract occurrence, relatively few neuromotor and neurosensory problems were reported by survivors of HCT performed in childhood. We did, however, find increased risk for motor impairments, hearing loss, vision loss, and persistent pain, suggesting the need for further investigation to understand the causes. As described in adult HSCT patients, cataracts are a frequent adverse effect of HSCT performed in childhood, occurring in 38% of our study population during the followup period. Close monitoring with appropriate intervention for preservation of vision, particularly among those who received TBI, should be a primary goal in survivors of childhood HSCT.

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