ASBMT
American Society for Blood and Marrow Transplantation

Osteochondroma after Hematopoietic Stem Cell Transplantation in Childhood. An Italian Study on Behalf of the AIEOP-HSCT Group

Maura Faraci,[1] Francesca Bagnasco,[2] Paola Corti,[3] Chiara Messina,[4] Franca Fagioli,[5] Marta Podda,[6] Arcangelo Prete,[7] Desirè Caselli,[8] Edoardo Lanino,[1] Giorgio Dini,[1] Roberto Rondelli,[7] Riccardo Haupt,[2] on behalf of the AIEOP-HSCT Group

A retrospective study was conducted among Italian children treated with hematopoietic stem cell transplant (HSCT) to evaluate the incidence and risk factors in the development of osteochondroma (OC). OC occurred in 27 patients who received autologous or allogeneic HSCT. The estimated 5-, 10-, and 15-year cumulative risk of developing OC was 0.5%, 3.2%, and 6.1%, respectively. Analysis of cumulative risk stratified by the various risk factors revealed that male sex ($P = .026$), autologous HSCT ($P = .001$), age at HSCT (≤ 3 years) ($P < .0001$), and total body irradiation (TBI) ($P < .0001$) significantly affected the risk of OC. Multivariate analysis, restricted only to tumor types with at least 1 case of OC, showed that earlier age at HSCT ($P = .0004$) and TBI ($P < .0001$) were the only factors that were significantly associated with OC.

Biol Blood Marrow Transplant 15: 1271-1276 (2009)

KEY WORDS: Osteochondroma, Total-body irradiation, Younger age, Autologous HSCT

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) represents the therapeutic choice for curing some types of malignant and nonmalignant diseases. However, although we attempt to cure the patient, the high-dose chemo- and radiotherapy that are administered may increase the risk of side effects on virtually any organ or system. In particular, the main skeletal complications observed in HSCT survivors are osteoporosis, avascular necrosis, and benign or malignant bone tumors.

Osteochondroma (OC) is the most common benign bone tumor that may develop in any bone where growth occurs by endochondral ossification. The metaphyseal regions of the long bones are the most frequently affected, and the distal femur, as well as the proximal tibia or humerus are the most common localizations. OC generally presents as a single lesion; however, multiple occurrences may develop in the context of hereditary multiple osteochondromatosis [1].

Only a few reports are currently available on OC occurrence in cancer survivors [2-4]. Most of them are case reports or case series, or refer to selected populations exposed to radiotherapy in whom a high incidence of OC has been reported. The only manuscript that analyzed a large cohort of transplanted patients, regardless of the conditioning regimen they received, did not demonstrate that total body irradiation (TBI) had any significant effect, whereas only autologous HSCT was found to be significantly associated with high OC risk [3]. Some authors suggested that the use of growth hormone (GH) replacement therapy in patients treated with TBI may increase the incidence of OC [5].

To further evaluate the incidence of OC after HSCT in a large cohort of transplanted children, and to assess the effect of various risk factors, we reviewed data from nine Italian HSCT centers of the Italian Association of Pediatric Oncology and Oncology (AIEOP).

From the [1]Department of Hematology-Oncology, Bone Marrow Transplant Unit, G. Gaslini Children's Hospital, Genova, Italy; [2]Epidemiology and Biostatistics Section, Scientific Directorate, G. Gaslini Children's Hospital, Genova, Italy; [3]Bone Marrow Unit, Clinic of Pediatrics, University of Milano Bicocca, San Gerardo Hospital, Monza, Italy; [4]Clinic of Pediatric Hematology Oncology, Department of Pediatrics, University of Padova, Padova, Italy; [5]Clinic of Pediatric Hematology Oncology, Department of Pediatrics, Regina Margherita Pediatric Hospital, Torino, Italy; [6]Pediatric Oncology Unit, Foundation IRCSS, Institute National of Tumors, Milano, Italy; [7]Department of Pediatrics, University of Bologna, Sant'Orsola Hospital, Bologna, Italy; and [8]DAI, Oncology-Oncology and Home Care, AUO Mayer, Firenze, Italy.

Financial disclosure: See Acknowledgments on page 1276.

Correspondence and reprint requests: Maura Faraci, MD, Department of Oncology/Oncology, Stem Cell Transplantation Section, G. Gaslini Children's Hospital, Largo G. Gaslini, 5; 16147 Genova, Italy (e-mail: maurafaraci@ospedale-gaslini.ge.it).

Received April 6, 2009; accepted June 4, 2009

1083-8791/09/1510-0007$36.00/0
doi:10.1016/j.bbmt.2009.06.003

Design and Methods

All children transplanted at any of the 21 AIEOP-HSCT centers, included in the Italian HSCT Registry, and who survived at least 1 year after transplant, were eligible for this study.

Data were available from the AIEOP-HSCT Registry, which collects prospectively information on demographics, type of primary diagnosis, date and type of transplant, conditioning regimen, occurrence and grade of acute and chronic graft-versus-host disease (aGVHD, cGVHD), date and status at last follow-up, and date of any second transplant. For the purposes of this study, primary diagnoses were grouped into 3 categories (ie, solid tumors, hematologic malignancies, and nonmalignant diseases), whereas 2 types of HSCT were defined (ie, autologous and allogeneic), and last, 2 categories based on age at HSCT were identified using 3 years of age as the cut off, ie, >3 or <3 years of age. With regard to data on conditioning regimens, they were grouped into 2 categories based upon the administration or absence of administration of TBI. Data regarding type of chemotherapy were not taken into consideration because drugs and schedules changed a great deal throughout the study period.

Specifically for this study, each center was required to report on all eligible patients in whom OC was diagnosed during follow-up. In case of OC, data were further collected on the date of OC, modality of diagnosis, site of OC, previous therapy with GH, clinical approach, and need for surgical treatment. As for methods of diagnosis, it could have been accidental or on clinical bases. In more detail, OC was accidental if observed after radiologic imaging performed for other reasons (eg, bone age, standard chest X-ray, or to exclude bone metastases), or on clinical bases if imaging (standard X-ray) was performed after patients complain of symptoms (eg, bone deformities, vascular or neurologic compromise, or mechanical joint problems).

This retrospective study was approved by the AIEOP-HSCT board, and data were collected anonymously. Moreover, all the HSCT patients or their guardians had previously signed a consent form allowing us to use their data for clinical research purposes. The procedures we followed were in accordance with the ethical standards and with the Helsinki Declaration. On the basis of Italian rules, no specific informed consent was required for this study.

Statistical Analysis

Descriptive statistics were reported in terms of absolute frequencies and percentages for qualitative data, and the Pearson's chi-square test or Fisher's exact test, if appropriate, were applied to compare proportions. Quantitative data were described in terms of median values and range because of their nonnormal (Gaussian) distribution. Accordingly, comparisons between groups were performed by the nonparametric Mann-Whitney *U*-test (MW), or by the Kruskal-Wallis (KW) test when >2 groups had to be compared.

Follow-up was censored at the date of the last follow-up or at the date of second HSCT (for patients who received more than 1 transplant). The cumulative risk of OC after HSCT was evaluated by the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. The Cox proportional hazard model was used for modeling the combined effect of the various prognostic factors. Because GVHD can only occur in allogeneic recipients, it was not included in the multivariable analysis of this model. The hazard ratio (HR) with the 95% CI was calculated to measure the effect of each predictor compared to the reference value, and the likelihood ratio test (LRT) was used to assess the effect of predictors. Proportional hazard assumption was tested using scaled Schoenfeld residuals against log of time.

All tests were 2 tailed and a P value $< .05$ was considered statistically significant. The statistical software "Statistica" (release 6.0, StatSoft Corporation, Tulsa, OK) and the software "Stata" (release 7.0, StataCorp 2001, College Station, TX) were used for all the analyses.

RESULTS

Nine of the 21 AIEOP-HSCT centers (43%) agreed to participate in this study. However, alone they had performed 56% (n = 3469) of the 6180 Italian transplants registered during the study period. These centers provided the data for the 1632 children who were eligible for this study, and among them a total of 27 OC (1.6%) were reported.

Table 1 reports the characteristics of patients stratified by OC status. Compared to children without OC, those with OC were more likely to be males (81%; n = 22; versus 59%; n = 942; $P = .017$), to be younger at diagnosis (median age 2.7 years versus 5.2 years; $P = .0003$), and at HSCT (median age 4.3 years versus 7.7 years; $P < .0001$), and to have received TBI as part of their conditioning regimen (96% $n = 26$; versus 37% n = 570; $P < .001$). No differences between children with or without OC were found with regard to underlying disease ($P = .065$), donor type ($P = .060$), and aGVHD or cGVHD ($P = .687$ and $P = .475$, respectively). As for the tumor type, among children with solid tumors, all the OC cases had had neuroblastoma (NB). As shown in Table 2, OC occurred in 6 (37%) of the 16 NB patients irradiated when ≤3 years old, and in 4 (10%) of those irradiated thereafter. Among children with other solid tumors, none were irradiated when ≤3 years old and none (0%) of the 6 irradiated when >3 years old developed OC. As for hematologic diseases, similar to NB patients, 5 (20%) of the 25 children irradiated before the age of 3 years developed OC.

Table 1. Characteristics of 1632 Patients Undergoing HSCT at 9 AIEOP-HSCT Centers

	Entire Cohort	Patients with OC	Patients without OC	*P**
Sex, n (%)				.017
Male	964 (59)	22 (81)	942 (59)	
Female	668 (41)	5 (19)	663 (41)	
Median age at diagnosis, years (range)	5.1 (−0.2†-18.2)	2.7 (0.4-10.3)	5.2 (− 0.2-18.2)	.0003
Median age at OC, years (range)	—	13.3 (3.9-21.5)	—	—
Median interval OC-HSCT, years (range)	—	8.9 (1.9-13.8)	—	—
Median age at HSCT, years (range)	7.6 (0.1-18.9)	4.3 (0.7- 10.6)	7.7 (0.1-18.9)	<.0001
Age at HSCT, n (%)				<.001
> 3 years	1391 (85)	15 (56)	1376 (86)	
≤ 3 years	241 (15)	12 (44)	229 (14)	
Underlying diseases, n (%)				.065
Solid tumors	624 (38)	10 (37)	614 (38)	
NB	*296 (47)*	*10 (100)*	*286 (47)*	
Bone tumors	*116 (19)*		*116 (19)*	
CNS tumors	*82 (13)*		*82 (13)*	
HD	*44 (7)*		*44 (7)*	
Soft tissue sarcomas	*38 (6)*		*38 (6)*	
Wilms tumor	*32 (5)*		*32 (5)*	
Other solid tumors	*16 (3)*		*16 (3)*	
Hematologic malignancies	798 (49)	17 (63)	781 (49)	
ALL	*421 (53)*	*8 (47)*	*413 (53)*	
AML	*242 (30)*	*6 (35)*	*236 (30)*	
NHL	*60 (8)*	*2 (12)*	*58 (7)*	
CML	*41 (5)*	*1 (6)*	*40 (5)*	
MDS	*19 (2)*		*19 (3)*	
Histiocytosis	*15 (2)*		*15 (2)*	
Nonmalignant diseases	210 (13)	0	210 (13)	
Inborn errors	*141 (67)*		*141 (67)*	
SAA	*69 (33)*		*69 (33)*	
Donor type, n (%)				.060
Autologous	856 (52)	19 (70)	837 (52)	
Allogeneic	776 (48)	8 (30)	768 (48)	
HLA identical related donor	*492 (63)*	*6 (75)*		
Unrelated donor	*242 (31)*			
HLA mismatched-related donor	*37 (5)*	*1 (12.5)*		
Syngenic	*5 (1)*	*1 (12.5)*		
TBI, n (%)				<.001
No	1036 (63)	1 (4)	1035 (64)	
Yes	596 (37)	26 (96)	570 (36)	
Acute GVHD,‡ n (%)				.687
No	175 (25)	1 (12)	174 (26)	
Yes	512 (75)	7 (88)	505 (74)	
Chronic GVHD,§ n (%)				.475
No	433 (63)	4 (50)	429 (63)	
Yes	252 (37)	4 (50)	248 (37)	
Total	1632	27	1605	—

ALL indicates acute lymphoblastic leukemia; NB, neuroblastoma; AML, acute myelogenous leukemia ; CNS tumors, central nervous system tumors; SAA, severe aplastic anemia; NHL, Non-Hodgkin lymphoma; HD, Hodgkin lymphoma; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; TBI, total body irradiation; GVHD, graft-versus-host disease; OC, osteochondroma; HSCT, hematopoietic stem cell transplantation.

*Pearson's chi-square or Fisher's exact test or Mann-Whitney *U*-test were used to compare the two groups of patients with and without OC.

†One patient with Neuroblastoma had prenatal diagnosis.

‡Evaluable for 776 allogeneic donors, 89 missing data.

§Evaluable for 776 allogeneic donors, 91 missing data.

Among children with OC, the diagnosis had been based on clinical symptoms in 16 of them (59%): 13 had had bone protuberances, and 3 complained of peripheral neurologic symptoms (paraesthesia). Diagnosis was accidental in the remaining 11 patients (41%), that is, following X-ray examination performed to evaluate bone age (n = 3), pulmonary disease (n = 2), bone metastases (n = 1), orthopedic problems (n = 1), or for other unspecified causes (n = 4).

OC occurred as a single lesion in the majority of patients (n = 17; 63%), while multiple lesions (range: 2-6) were identified in 10 patients. Overall, a total of 43 localizations were described as follows: 39 (91%) in the metaphyseal region of the long bones (14 femurs; 10 tibias; 5 ribs; 5 fibulas; 3 radii; and 2 ulnas) and 4 (9%) in flat bones (2 iliac bones; 1 metacarpus; and 1 scapula).

None had a family history of OC. Three patients had received GH replacement therapy and they developed OC 0.1, 0.8, and 3.2 years after GH therapy, and 5.1, 8.7, and 9.7 years after HSCT, respectively.

In general, a wait-and-see or symptomatic therapeutic approach was applied to all patients. Surgery

Table 2. Distribution of TBI by Underlying Diseases among 241 Children at ≤3 Years of Age Since HSCT and 1391 Children at >3 Years of Age Since HSCT

	Age at HSCT ≤3 Years		Age at HSCT >3 Years	
Underlying diseases	TBI Yes, n (n OC, %)	TBI No, n (n OC, %)	TBI Yes, n (n OC, %)	TBI No, n (n OC, %)
NB	16 (6, 37)	74 (0)	42 (4, 10)	164 (0)
Other solid tumors	0 (0)	20 (0)	6 (0)	302 (0)
Hematologic malignancies	25 (5, 20)	65 (1, 1)	504 (11, 2)	204 (0)
Nonmalignant diseases	1 (0)	40 (0)	2 (0)	167 (0)
Total	42 (11, 26)	199 (1, 1)	554 (15, 3)	837 (0)

TBI indicates total body irradiation; NB, neuroblastoma; OC, osteochondroma; HSCT, hematopoietic stem cell transplantation.

was performed only if severe clinical problems occurred, such as intractable bone pain, or compression on nervous-vascular structures. At follow-up, 5 subjects (19%) had undergone surgical OC resection after a median of 9 months (range: 0-4.8 years). None had malignant evolution of OC.

Length of follow-up after HSCT ranged between 1.1 and 29.1 years (median, 4.8 years). The estimated 5-, 10-, and 15-year cumulative risk of developing OC for the entire cohort was 0.5% (95% confidence interval [CI] 0.2-1.3), 3.2% (95% CI 2.1-5.1), and 6.1% (95% CI 4.0-9.1), respectively (Figure 1). Stratification of the analysis by various risk factors showed that male sex, young age at HSCT, treatment with TBI, and autologous type of HSCT were statistically significant risk factors for OC (Table 3). In more detail, and considering the cumulative risk at 15 years after HSCT, the probability of developing OC was 8.6% for males versus 2.1% for females ($P = .026$); 20.2% for children transplanted at age ≤3 years versus 3.9% among those transplanted later ($P < .001$); 12.1% for patients treated with TBI versus 0.2% for those who did not receive TBI ($P < .001$); 11.8% for

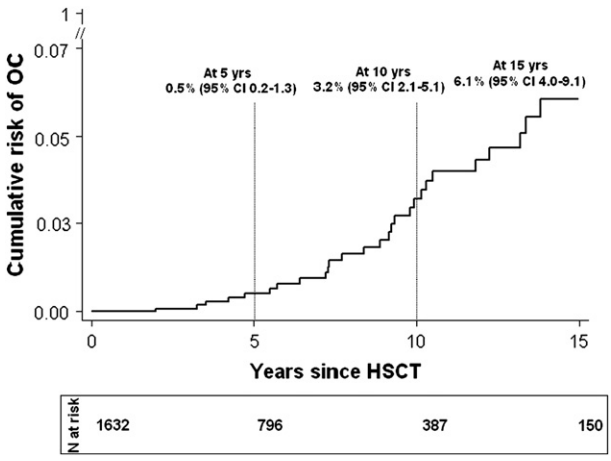

Figure 1. Estimated 15-year cumulative risk (Kaplan-Meier failure estimate) of developing OC after HSCT.

autologous recipients versus 2.7% among allogeneic recipients ($P = .001$). With regard to the underlying disease, there was a significant difference in the probability to develop OC across the 3 disease categories evaluated ($P = .006$). This difference remained significant also if categories in which no OC were documented (ie, nonmalignant hematologic diseases and solid tumors other than NB) were excluded from the analysis (data not shown).

The type of underlying disease was not taken into consideration in the Cox proportional hazard model of the entire cohort (Table 4), in particular, because of the absence of OC events among patients with nonmalignant diseases and solid tumors other than NB. In this model, only age at HSCT, type of HSCT, and TBI were found to be significantly associated with an increased risk of OC. In more detail, children transplanted at a younger age (≤3 years) had a 6.08-fold (95% CI 2.78-13.29) increased risk of OC. If type of HSCT was evaluated, patients who received autologous HSCT had a 2.67-fold (95% CI 1.13-6.25) increased risk of OC compared to those who received allogeneic HSCT. Finally, we confirm that TBI significantly affects the probability of OC, with a 32.99-fold (95% CI 4.44-245.42) increased OC risk among children treated with TBI. In a further analysis, the Cox model was restricted to the only 2 tumor categories in which at least 1 OC was reported (ie, NB and hematologic malignancies). Also in this model, age at HSCT and TBI remained as the only significant risk factors. The effect of NB was not significant ($P = .3995$), even if NB patients had a 1.53 HR compared to children with hematologic disease.

DISCUSSION

To our knowledge, this is largest series of transplanted children in which the risk factors for OC following HSCT have been analyzed. Moreover, this cohort has been followed up for a longer period of time (median 4.8 years) compared to what has been (2.6 years) reported in the other large cohort described to date [3].

Even though univariate analyses showed that several factors were significantly related to the risk of developing OC, multivariate analyses revealed that young age at transplant and treatment with TBI were the only independent risk factors significantly related to the probability of developing OC. Autologous transplant was also found to be an independent risk factor, but with a less significant value, and only when the entire cohort was analyzed. We believe that autologous transplant was a confounding factor and that our finding was not because of the procedure "per se," but to the fact that in our series, 95% of the patients who developed OC after autologous HSCT

Table 3. Cumulative Risk of Developing OC in 1632 HSCT Patients, Shown by Various Risk Factors

Risk Factor	No. of OC (%)	%Cumulative Risk (95%CI)			*P*
		At 5 Years	At 10 Years	At 15 Years	
Sex					.026
Male	22 (81)	0.5 (0.2-1.6)	4.0 (2.3- 6.7)	8.6 (5.4-13.3)	
Female	5 (19)	0.5 (0.1-2.2)	2.1 (0.8- 5.1)	2.1 (0.8- 5.1)	
Underlying disease					.006
Solid tumors	10 (37)	0.0	6.6 (3.1-13.7)	12.9 (6.4-25.2)	
Hematologic	17 (63)	0.9 (0.4-2.3)	3.3 (1.8- 5.9)	6.8 (3.9-11.5)	
Nonmalignant	0	—	—	—	
Age at HSCT					<.001
≤3 years	12 (44)	1.3 (0.3-4.9)	13.3 (7.1-24.1)	20.2 (10.9-35.6)	
>3 years	15 (56)	0.4 (0.1-1.2)	1.6 (0.8- 3.1)	3.9 (2.2- 6.7)	
TBI					<.001
No	1 (4)	0.2 (0.1-1.2)	0.2 (0.1-1.2)	0.2 (0.1-1.2)	
Yes	26 (96)	0.9 (0.4-2.6)	6.6 (4.1-10.4)	12.1 (8.1-17.9)	
Donor type					.001
Autologous	19 (70)	0.4 (0.1-1.8)	6.5 (3.8-11.1)	11.8 (7.2-18.9)	
Allogeneic	8 (30)	0.6 (0.2-1.8)	1.1 (0.5-2.8)	2.7 (1.3-5.8)	
Acute GVHD					.489
No	1 (12)	0.8 (0.1-5.3)	0.8 (0.1-5.3)	0.8 (0.1-5.3)	
Yes	7 (88)	0.6 (0.2-2.5)	1.6 (0.6-4.2)	4.8 (2.1-11.1)	
Chronic GVHD					.427
No	4 (50)	0.7 (0.2-2.7)	0.7 (0.2-2.7)	3.7 (1.1-11.3)	
Yes	4 (50)	0.7 (0.1-4.7)	2.7 (0.8-8.2)	4.2 (1.5-11.3)	
Total	27	0.5 (0.2-1.3)	3.2 (2.1-5.1)	6.1 (4.0- 9.1)	—

TBI, total body irradiation; GVHD, graft-versus-host disease; CI, confidence interval; HSCT, hematopoietic stem cell transplantation; OC, osteochondroma.

had also received TBI, and that 60% of them were ≤3 years old at the time of transplant. Among these patients, 60% had had NB and had been treated before 1991 when the conditioning regimens for that disease included TBI. This procedure is no longer in use, and therefore we postulate that this finding will not be confirmed when longer follow-up will be available for children more recently treated with autologous HSCT, but with no TBI-containing regimens. This observation is further confirmed by the Cox analysis restricted to only tumor types in which at least 1 case of OC was documented (ie, NB and hematologic malignancies) and in which type of transplant was no more significant. In this analysis also the NB was not found to be a risk factor for OC.

Most of the reports on OC after HSCT refer to selected populations (eg, those treated with TBI [2,4] or any type of radiation [6]). These authors reported that younger children (<5 years [2] or <8 years [7]) are at higher risk of radiation-induced OC. On the other hand, the only other study that included all transplanted children was the 1 by Bordigoni et al. [3], who found autologous transplant to be the only significant risk factor. This study was based on 8 cases of 249 transplanted children conditioned either with TBI or busulfan (Bu).

We believe that our study, which is the largest reported to date, is useful to confirm the detrimental effect of TBI, in particular, when given at a younger age. In fact, the skeletal damage caused by TBI, especially when administered at a young age is recognized [2,8]. Because TBI leads to growth impairment through peripheral lesions to the bones and cartilage, the epiphysis remains open longer than usual, thus allowing more time for OC to develop [6].

Another observation regards our estimation of a 6.1% cumulative risk of developing OC 15 years after transplant. In particular, we observed an 11.8 % cumulative risk after autologous HSCT and only 2.7% cumulative risk after allogeneic HSCT. These results are lower compared to estimates by Bordigoni et al. [3], who reported a 31.7% and 13.0% 12-year cumulative risk after autologous and allogeneic transplant, respectively. We suggest that these differences might be because of a possible underreporting bias in our multicenter study, but also to the fact that our study includes all types of conditioning regimens, unlike Bordigoni et al. [3], who only took into consideration regimens including either TBI or Bu.

Last, in our series we did not document any malignant degeneration of OC. This event is described as occurring more frequently in case of hereditary multiple osteochondromatosis (2.5%) [1]. Moreover, the only 3 reported patients who underwent malignant transformation of OC had also previously received local high-dose irradiation to treat their solid tumors [5,9,10].

Harper et al. [11] and Bordigoni and colleagues [3] suggested that children treated with GH replacement therapy had a tendency to develop early OC and after less time following HSCT, because GH therapy might be a trigger feature in radiotherapy-disturbed epiphyses. Sanders et al. [5] demonstrated that patients receiving GH developed OC after a longer period of

Table 4. Multivariate Analysis on the Effect of Various Risk Factors on the Hazard Function of Developing OC in 1632 HSCT Patients and in 1094 HSCT Patients with NB or Hematologic Malignancies

Entire Cohort				
Factor	HR	CI 95%	LR	*P*
Sex			3.14	.0762
Female	1.00			
Male	2.26	0.85-6.03		
Age at HSCT			17.59	<.0001
>3 years	1.00			
≤3 years	6.08	2.78-13.29		
Donor type			5.49	.0191
Allogeneic	1.00			
Autologous	2.67	1.13-6.25		
TBI			33.48	<.0001
No	1.00			
Yes	32.99	4.44-245.42		
LRT of model = 65.4; P < .0001				
Only patients with NB or Hematologic Malignancies				
Factor	HR	CI 95%	LR	*P*
Sex			2.81	.0937
Female	1.00			
Male	2.18	0.82-5.80		
Age at HSCT			12.31	.0004
>3 years	1.00			
≤3 years	5.08	2.14-12.10		
Donor type			2.83	.0926
Allogeneic	1.00			
Autologous	2.27	0.88-5.87		
TBI			18.67	<.0001
No	1.00			
Yes	18.23	2.41-137.65		
Underlying disease			0.71	.3995
Hematologic	1.00			
NB	1.53	0.57-4.10		
LRT of model = 44.2; *P* < .0001				

TBI indicates total body irradiation; HSCT, hematopoietic stem cell transplantation; CI, confidence interval; HR, hazard ratio; NB, neuroblastoma; LR, likelihood ratio; LRT, likelihood ratio test; OC, osteochondroma.

time following HSCT, but they were younger at HSCT than non-GH treated patients. In our experience, only 3 patients with OC had received GH replacement therapy, and none of them developed malignant degeneration of their OC. Unfortunately, however, we could not provide any information on the GH-related risk of developing OC because this information was not available in the Italian HSCT registry.

Regarding the guidelines for monitoring OC, we agree with Taitz et al. [2], who believe that annual or biannual screening by plain radiologic examination is not cost-effective, and that furthermore, it is dangerous (exposure to further radiation) and psychologically harmful. We believe that only careful clinical evaluation and follow-up, especially in patients treated with TBI at a young age, would be useful for the early diagnosis of OC , as well as to evaluate the need for surgical treatment.

ACKNOWLEDGMENTS

M.F. and R.H. contributed to the design, conduction, and analysis of the study and wrote the paper; F.B., R.H., with R.R. contributed to statistical analysis, data entry, and collection of patients in the AIEOP registry; M.F., P.C., C.M., F.F., M.D., A.P., D.C., E.L., and G.D. contributed to data collection, interpretation of results, and critically reviewing the manuscript.

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Bovée JV. Multiple osteochondromas. *Orphanet J Rare Dis*. 2008;13:3.
2. Taitz J, Cohn RJ, White L, Russell SJ, Vowels MR. Osteochondroma after total body irradiation: an age-related complication. *Pediatr Blood Cancer*. 2004;42:225-229.
3. Bordigoni P, Turello R, Clement L, et al. Osteochondroma after pediatric hematopoietic stem cell transplantation: report of eight cases. *Bone Marrow Transplant*. 2002;29:611-614.
4. Maeda G, Yokoyama R, Ohtomo K, et al. Osteochondroma after total body irradiation in bone marrow transplant recipients: report of two cases. *Jpn J Clin Oncol*. 1996;26:480-483.
5. Sanders JE, Guthrie KA, Hoffmeister PA, Woolfrey AE, Carpenter PA, Appelbaum FR. Final adult height of patients who received hematopoietic cell transplantation in childhood. *Blood*. 2005;105:1348-1354.
6. Marcovici PA, Berdon WE, Liebling MS. Osteochondromas and growth retardation secondary to externally or internally administered radiation in childhood. *Pediatr Radiol*. 2007;37:301-304.
7. Fletcher BD, Crom DB, Krance RA, Kun LE. Radiation-induced bone abnormalities after bone marrow transplantation for childhood leukemia. *Radiology*. 1994;191:231-235.
8. Cohen A, Rovelli A, Bakker B, et al. Final height of patients who underwent bone marrow transplantation for hematological disorders during childhood: a study by the Working Party for Late Effects-EBMT. *Blood*. 1999;93:4109-4115.
9. Mahboubi S, Dormans JP, D'Angio G. Malignant degeneration of radiation-induced osteochondroma. *Skeletal Radiol*. 1997;26:195-198.
10. Eagleton MD, Seaman WB. Radiation therapy of neuroblastoma. *Radiology*. 1957;68:1-8.
11. Harper GD, Dicks-Mireaux C, Leiper AD. Total body irradiation-induced osteochondromata. *J Pediatr Orthop*. 1998;18:356-358.