Bone Marrow Transplantation (2002) 29, 611–614

www.nature.com/bmt

Second malignancies

Osteochondroma after pediatric hematopoietic stem cell transplantation: report of eight cases

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Summary:

Eight children developed osteochondroma (OS) at a mean of 88 months after hematopoietic stem cell transplantation (HSCT). The mean age at HSCT was 56 months (12–84). This represents a cumulative incidence of 20% among patients less than 18 years of age transplanted from 1981 to 1997. These eight patients underwent allogeneic ($n = 2$) or autologous ($n = 6$) transplantation for either acute leukemia ($n = 6$) or neuroblastoma ($n = 2$) after a conditioning regimen including TBI ($n = 7$) or a combination of Bu and CY. OS was multiple in seven patients and solitary in one. Eight lesions were resected and all were benign. Four children received growth hormone before diagnosis of OS, but there was no clinical, radiological or histological difference between those who did not. Univariate analysis showed an increased rate associated only with autologous HSCT, with a 31.7% probability of a new OS at 12 years after HSCT. Osteochondroma should be added to the other adverse effects of HSCT in children.
Bone Marrow Transplantation (2002) **29,** 611–614. DOI: 10.1038/sj/bmt/1703424
Keywords: osteochondroma; hematopoietic stem cell transplantation; children

Hematopoietic stem cell transplantation (HSCT) is a life-saving treatment for children with potentially fatal diseases such as hematological malignancies, severe aplastic anemias, inherited diseases or neuroblastomas. As the expected cure rate can reach 30 to 70% in children, quality of life in long-term survivors should be carefully monitored. Agents used include high-dose cyclophosphamide in combination with busulfan or with total body irradiation. These regimens may affect neuroendocrine function, particularly thyroid function, growth, puberty and fertility. Cataract, airway and pulmonary disease, secondary malignancies and musculo-skeletal problems are also frequent complications.[1,2] Among these latter, osteochondroma have been reported only rarely,[3–6] although this condition is well-known after local irradiation in children.[7–10]

We report eight children who developed an osteochondroma following HSCT.

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Received 11 June 2001; accepted 9 January 2002

Materials and methods

Patient characteristics (Table 1)

We studied eight children (ages at diagnosis: 1–7 years (mean: 4 years 8 months) and at HSCT: 1 year 8 months–11 years 4 months (mean: 6 years 2 months)) who underwent transplantation between May 1981 and December 1997. These eight patients were identified among 156 consecutive allogeneic HSCT and 93 consecutive autologous HSCT performed during this period. All the patients were less than 18 years of age at the time of transplantation. Five received HSCT for acute lymphoblastic leukemia (ALL) while in first complete remission (CR) (patients 2, 3 and 5) or in CR2 (patients 1 and 7). One received transplantation for acute myeloid leukemia (AML) while in CR2 (patient 8) and two for stage 4 neuroblastoma, either in CR (patient 6) or in partial remission (patient 4). They received either autologous HSCT ($n = 6$) or HSCT from matched sibling donors ($n = 2$).

Conditioning regimens

Conditioning regimens are described in Table 1. Briefly, TBI was delivered using 12 Gy in six doses of 2 Gy, in two fractions per day for 3 consecutive days, or 13.2 Gy in eight doses of 1.65 Gy, in three fractions per day for 3 consecutive days. The eighth patient received 10 Gy given in a single fraction with an average dose rate of 17.7 cGy/min. TBI was followed by high-dose chemotherapy: CY, or high-dose aracytine and melphalan.

The last patient with neuroblastoma was given busulfan in addition to melphalan. Finally, two children had received prior cranial (24 Gy) (No. 1) or cranio-spinal (18 Gy) (No. 5) irradiation as part of their initial therapy.

Table 1 Patient characteristics

Patient No.	*Age at HSCT/sex*	*Primary disease*	*Latency post HSCT (month)*	*Conditioning regimen*	*Type of HSCT*	*GHT*[a]	*GVHC*[b]
1	11 y 4 mo/M	ALL	156	TBI 13.2 Gy + CY[c] + Ara-C[d] + VP16[e]	ABMT	yes (14–74)	
2	4 y 5 mo/M	ALL	126	TBI 12 Gy + CY +TLI[f] 4 Gy	geno-id[l]	no	no
3	5 y 2 mo/M	ALL	88	TBI 12 Gy + CY	geno-id	yes (48–120)	no
4	4 y 3 mo/M	NEURO[k]	112	TBI 12 Gy + Mel[g]	ABMT	yes (30–100)	
5	9 y 8 mo/M	ALL	27	TBI 12 Gy + Ara-C[h] + Mel[g]	ABMT	no	
6	1 y 8 mo/M	NEURO	58	Bu[i] + Mel[g]	ABMT	no	
7	7 y/M	ALL	42	TBI 12 Gy + Ara-C[h] + Mel[g]	ABMT	no	
8	4 y 2 mo/M	AML	99	TBI 13.2 Gy + CY	ABMT	yes (42–100)	

[a]Growth hormone replacement therapy started at a mean dose of 13 U/m^2/week by daily subcutaneous injections and increased to a mean of 18 U/m^2/week (times onset and end after HSCT in months); [b]chronic GVHD; [c]i.v. 60 mg/kg once daily for 2 days; [d]i.v. 1 g/m^2; [e]i.v. 600 mg/m^2; [f]total lymphoid irradiation; [g]melphalan: i.v. (140 mg/m^2); [h]3 g/m^2 every 12 h i.v. for four or eight doses; [i]37.5 mg/m^2, p.o., in four divided doses daily for 2 days; [k]neuroblastoma; [l]geno-identical HSCT.

GVHD prophylaxis

GVHD prophylaxis included methotrexate and cyclosporin A for patient No. 3 and T cell depletion of the marrow for patient No. 2. Neither of these two children developed acute or chronic GVHD.

Other patient characteristics (Table 1)

All children were in sustained CR with a median follow-up of 11 years (1.5–16). Four patients received replacement therapy with growth hormone (GHT) starting at a median elapsed time of 68.5 months (range, 40–142) before the occurrence of the OS. None of the patients had a clinically detectable bony mass before HSCT or a family history of hereditary multiple exostoses.

Skeletal study

Skeletal studies (radiography) were performed for specific physical complaints or for routine follow-up (bone age determination). In addition, three patients had computed tomography scans and two had magnetic resonance imaging for the skeletal survey.

Statistical analysis

We assessed the risk of new OS in 249 children transplanted between 1981 and 1997 in our unit (autologous HSCT, $n = 93$; allogeneic HSCT, $n = 156$; busulfan-based regimens, $n = 115$; TBI based regimens, $n = 134$; ALL, $n = 108$; AML, $n = 43$; neuroblastoma, $n = 24$; other, $n = 74$). Moreover, 20 patients received GH treatment for radiation-induced growth failure associated with GH insufficiency (busulfan-based regimens, $n = 6$; TBI-based regimens, $n = 14$; autologous HSCT, $n = 8$; allogeneic HSCT, $n = 12$).

Kaplan–Meier product-limit estimates with a 95% confidence interval were used to estimate the projected incidence of OS. The log-rank procedure was used to assess the statistical significance of differences between subgroups of children. Means were compared by Student's *t*-test, Fisher's exact test and the Wilcoxon rank test.

Results

Eight patients developed OS a mean of 88 months (range, 27–156) after HSCT. This represents a cumulative incidence of 20% among children less than 18 years of age at the time of transplantation surviving more than 3 years and transplanted during the period from 1981 to 1997. Mean follow-up after initial clinical presentation of the OS was 31 months (range, 2–71). Multiple OS were identified in seven patients and a solitary OS in one (No. 1). Locations included: clavicle (2), ribs (2), superior iliac epiphysis (1), metaphysis of the distal femur (2), distal (2) and proximal (1) tibia, proximal humerus (1), distal radii (3), scapula (3), proximal metaphysis of the proximal phalanges of the fingers (2) and parietal bone (1). OS were asymptomatic in four children. Eight lesions in five patients (1, 2, 3, 4 and 5) were resected and all were benign. The reasons for resection included pain, location and/or growth of the mass. There was no clinical, radiological or histological difference between patients who received GHT and those who did not.

Univariate analysis showed increased OS risk associated only with autologous HSCT. Kaplan–Meier estimates of the probability of new OS at 6, 10 and 12 years after HSCT were 6% and 0%; 20.2% and 13% and 31.7% and 13% (95% CI), respectively, for autologous and allogeneic HSCT ($P = 0.01$; RR = 14.3) (Figure 1). In contrast, the risk of new OS did not vary according to the type of conditioning regimen (TBI *vs* Bu-based regimens), type of primary disease (ALL, AML or neuroblastoma) or whether or not patients received GHT. Other possible prognostic factors including age had no significant effect on the outcome.

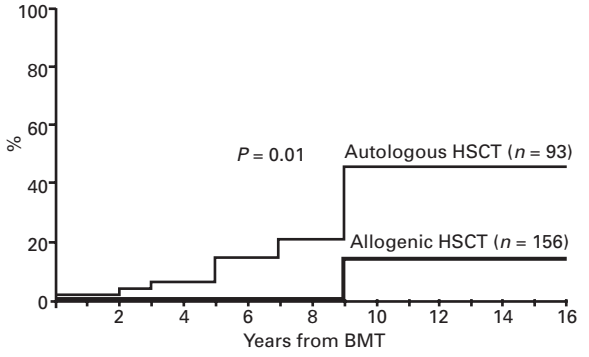

Figure 1 Actuarial probability of new osteochondromas by type of transplantation (AHSCT: autologous HSCT; allo HSCT: allogeneic HSCT).

Discussion

Recently, skeletal abnormalities including multiple OS, have been reported in young children who are long-term survivors after HSCT.[2–6] To our knowledge, there have been only 21 reported observations of OS essentially found in the long bones following HSCT (Table 2). All were in children aged less than 8 years at the time of transplantation and all had received TBI (fractionated in eight (12 Gy), single dose (7 Gy) in four, unknown fractionation in nine (9–14.4 Gy)) (Table 2) as part of the conditioning regimen. Only one patient had received previous radiation therapy within the context of his initial treatment. Sixteen were transplanted for hematological disorders, four for immunodeficiency disorders and one for a stage 4 neuroblastoma. Fifteen patients received bone marrow from siblings, four from haploidentical parents and two received autologous HSCT. The incidence ranged from 13.5% to 27%[2–6] (Table 2). Our data are somewhat different, as in our series one of the eight patients received busulfan instead of TBI, and autologous HSCT was a significant risk factor. The cumulative risk reached 31.7% 12 years after transplantation within this subgroup of children. In our population, OS were seen only in patients who received HSCT before they were 12 years old, but not in our adult patients (data not shown). For these children, GHT is often indicated although GH deficiency does not seem to play a major role in growth impairment after HSCT.[11] It has been claimed that GHT may increase the risk of tumor or leukemia recurrence.[12] However, the results of most studies suggest that GHT is not associated with an increased likelihood of disease relapse.[13] There is no report of OS developing following GHT,[14] however, two-thirds and one-half of Harper *et al*'s[6] and our patients respectively received GHT when OS was identified. Nevertheless, this did not reach statistical significance. A life-long follow-up of all patients surviving childhood HSCT would be required to obtain valid information about GH-induced secondary OS.

It appears that the dose of 12 Gy of TBI is sufficient to cause multiple OS in young children. However, the incidence in our series, particularly for patients receiving autologous HSCT, was considerably greater than the 1 to 12% reported frequency in the general population after local irradiation using median doses of 30 Gy at 2 Gy per day.[7–9] Perhaps fractionation and dose rate play a role. Moreover, one of our patients who developed two lesions 5 years after autologous HSCT for neuroblastoma, did not receive TBI but a combination of busulfan and melphalan. We lack data to assess the role of chemotherapy in this context. The development of OS after HSCT may possibly be attributable to more than one factor.

Further prospective studies will be necessary to establish the exact implications of the immunosuppressive effects of autologous or allogeneic transplantations in the development of multiple OS.

All the eight resected OS at our institution were benign. However, several cases of radiation-induced malignant exostosis have been reported after local radiotherapy.[15,16]

Table 2 Osteochondroma after bone marrow transplantation

Patient No. (Ref.)	*Age at HSCT/Sex*	*Primary disease*	*Latency*	*Conditioning regimen*	*Type of HSCT*	*GH*[c]	*GVHC*[h]	*Incidence (%)*
1[c]	8 mo/F	AML	9 y 3 mo	TBI + 12 Gy + CY	geno-id[e]	no	no	
2[c]	17 mo/F	AML	7 y 11 mo	TBI 12 y + HDArac	geno-id	no	no	
3[c]	22 mo/M	AML	10 y 2 mo	TBI 12 Gy + CY	geno-id	no	no	13.5
4[c]	27 mo/F	AML	11 y 2 mo	TBI 12 Gy + CY	geno-id	no	no	
5[c]	7 y 8 mo/M	AML	17 y 6 mo	TBI 12 Gy + CY	geno-id	no	no	
6[e]	3 y 1 mo/M	JCML	8 y 3 mo	TBI 12 Gy + U	geno-id	no	U[b]	16.7
7[e]	6 y 4 mo/M	AML	8 y 5 mo	TBI 12 Gy + U	ABMT	no		
8[d]	21 mo/M	NEURO[g]	9 y 6 mo	TBI 12 Gy + U	ABMT	no		U[b]
9–12[b]	U[b]	ID[a]	U[b]	TBI 7 Gy + CY	Haplo-id[f]	U[b]	U[b]	27
13[f]		ALL		TBI + CY (9–14.4 Gy)	geno-id			
14[f]		ALL		TBI + CY (9–14.4 Gy)	geno-id			
15[f]		ALL		TBI + CY (9–14.4 Gy)	geno-id			
16[f]	Mean age:	ALL	Mean:	TBI + CY (9–14.4 Gy)	geno-id			
17[f]	4 y (1–8)	ALL	6 y (1–11)	TBI + CY (9–14.4 Gy)	geno-id	6/8	1/8	23
18[f]		ALL		TBI + CY (9–14.4 Gy)	geno-id			
19[f]		ALL		TBI + CY (9–14.4 Gy)	geno-id			
20[f]		AML		TBI + CY (9–14.4 Gy)	geno-id			
21[f]		AML		TBI + CY (9–14.4 Gy)	geno-id			

[a]Immunodeficiency; [b]unknown; [c]growth hormone replacement therapy after HSCT; [d]high-dose aracytine; [e]geno-identical HSCT; [f]haplo-identical HSCT; [g]neuroblastoma; [h]chronic GVHD.

Moreover, the simultaneous occurrence of osteosarcoma and osteochondroma following autologous HSCT for neuroblastoma has been recently reported.[4] Even if the likelihood of malignant change is quite low, the generally increased risk of second malignancies, particularly in young children,[17] warrants continued skeletal survey of long-term survivors of childhood HSCT. Systematic biopsy or resection is not necessary and surgical treatment may be needed only when articular function or neurovascular structures are impaired.

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