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Dental abnormalities after pediatric bone marrow transplantation

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Summary:

Our purpose was to describe the types and frequencies of altered dental development in pediatric patients following bone marrow transplantation (BMT). A retrospective review of the medical records and panoramic radiographs of all patients who underwent BMT at St Jude Children's Research Hospital between 1990 and 2000, for whom pre-BMT and post-BMT dental examination and panoramic radiography records were available, is presented. All patients were treated on institutional protocols. We recorded patient demographics and radiographic evidence of microdontia, hypodontia, taurodontia, root stunting, caries, enamel pearls, dental restorations/extractions and pulpal calcification. The 99 patients identified (52 males, 47 females) had a median age of 13.5 years (range, 3.4–25.9 years) at the time of BMT. In all, 73 were Caucasian, 15 were African-American, and 11 were of other races. The frequency of radiographically evident root stunting in permanent teeth was significantly increased after BMT ($P<0.001$), but there was no significant change in the frequency of other dental abnormalities after BMT. Dental abnormalities are prevalent in survivors of childhood BMT, but only root stunting appeared to progress with BMT.
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As more children survive after bone marrow transplantation (BMT), due to advances in treatment, supportive care, and clinical application of research findings, studies of the long-term effects of therapy become important for the future health of survivors. BMT is increasingly used as therapy for children with malignant and nonmalignant disorders. It is used as primary or adjunctive therapy in the management of acute and chronic leukemia, aplastic anemia, severe combined immunodeficiency, metabolic disorders, Wiskott–Aldrich syndrome, Hodgkin's disease, solid tumors, and other diseases that directly or indirectly affect the bone marrow.[1–3] However, little information has been published about the late toxic effects of pediatric BMT, which may continue for the life of the patient.

Numerous studies have investigated the immediate effects of chemotherapy and/or radiation on the oral mucosa and other perioral soft tissues,[1–9] but few have addressed the late dental sequelae of cancer treatment received at an early age. Hypodontia, microdontia, enamel hypoplasia, root stunting, taurodontia, over-retention of primary teeth, and an increased caries index have been reported in survivors of childhood cancer.[10–13] Impaired root development reduces the growth of alveolar bone, which adversely affects the subsequent vertical development of the mandible and the lower one-third of the face.[14] Other reported abnormalities include malocclusion,[15] narrowing of the pulp canal,[16] and decreased temporomandibular joint mobility.[17] The purpose of this study was to describe the types and frequencies of altered dental development in pediatric patients who had undergone BMT.

Materials and methods

After approval by the Institutional Review Board and in compliance with the Health Information Portability and Accountability Act (HIPAA), the medical records and panoramic radiographs of all children who underwent BMT at St Jude Children's Research Hospital between 1990 and 2000 and who had panoramic radiographs obtained before and after BMT were reviewed. Routine pre-BMT dental examination had not been routinely obtained until the late 1990s. When performed, they were typically ordered only on children who were 3 years of age and older because of difficulty in younger children cooperating with completion of the radiograph. This cohort was included in part in a large series discussing the dental status of patients undergoing BMT preparation.

All radiographs were evaluated by a senior pediatric dental resident (MV), with the consistent supervision of a practicing pediatric dentist (CR). All radiographically apparent microdontia, hypodontia, taurodontia, root

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stunting, enamel pearls, caries, dental restorations/extractions, and pulpal calcifications were recorded. Abnormalities of the third molar were excluded because of the high rate of third-molar hypodontia and microdontia in otherwise healthy populations. Abnormalities of the bony structures and the temporomandibular joint were not assessed.

Results were statistically analyzed according to the type of teeth examined: primary teeth, permanent teeth, and mixed teeth. If patients had multiple dental examinations before or after BMT, information from the most recent examination was used. Eight abnormalities (microdontia, hypodontia, taurodontia, root stunting, enamel pearls, caries, dental restorations/extractions, and pulpal calcifications) were assessed. If patients had developed any one of the above, they would be defined as having abnormal teeth. The frequency of abnormality type was assessed by tooth type independently and the abnormality was counted only once if a patient had one or more abnormality of the same kind. Fisher's exact test was used to compare the proportion of patients who had dental abnormality before and after BMT by assuming that they were independent groups. For patients who had mixed dentition at the time of dental examination, information was recorded only for abnormal teeth and not for the total number of primary teeth and adult teeth examined; therefore, the results of analysis are exploratory and should be interpreted with caution. The many treatment regimens used for these patients precluded analysis of the relation of dental abnormalities to treatment regimens. However, we analyzed the potential effect of total body irradiation (TBI) by categorizing patients as having received or not having received TBI. We coded a history of graft versus host disease (GVHD) as yes or no.

Results

In all, 29% of all patients ($N = 340$) who received BMT during the study period underwent a dental examination with panoramic radiography both before and after BMT. Their median age at the time of BMT was 13.5 years (range, 3.4–25.9 years). In total, 52 patients were male; 73 were Caucasian, 15 were African-American, and 11 were of other races (Table 1). The primary diagnoses were leukemia ($n = 70$), aplastic anemia, or myelodysplastic syndrome ($n = 10$), neuroblastoma ($n = 7$), Hodgkin's disease ($n = 3$), non-Hodgkin's lymphoma ($n = 3$), sickle cell disease ($n = 2$), congenital immunodeficiency syndrome ($n = 2$), brain tumor ($n = 1$), and rhabdomyosarcoma ($n = 1$). The median time between the pre-BMT panoramic radiograph and BMT was 29 days (range, 7–1642 days), and the median time between BMT and the post-BMT radiograph was 3.08 years (range, 0.17–9.04 years).

Before BMT 56 (56.6%) of the 99 patients had abnormal dentition, while after BMT 79 (79.8%) had abnormal dentition. Among patients who had permanent dentition before or after BMT, these rates were 66.7% (38/57) and 82.2% (60/73), respectively (Table 1). No statistically significant increase was observed in any dental abnormality, except root stunting ($P < 0.001$).

Among patients who had mixed dentition at the time of their pre-BMT examination, an increase in the frequency of dental abnormalities was seen after BMT: 43.8% (14/32)

Table 1 Demographics and dental maturation of 99 patients who had dental examination both before BMT and after BMT

Patient characteristics	*Teeth type before BMT*			*Teeth type after BMT*			*Total (N = 99)*
	Primary teeth (N = 10)	*Permanent teeth (N = 57)*	*Mixed teeth (N = 32)*	*Primary teeth (N = 4)*	*Permanent teeth (N = 73)*	*Mixed teeth (N = 22)*	
Age at BMT							
Mean	5.07	15.99	8.29	7.75	14.36	6.71	12.39
s.e.	0.37	0.44	0.46	3.21	0.51	0.33	0.52
Median	5.28	15.56	8.19	5.15	14.68	6.17	13.50
Range	3.38–7.27	5.87–25.93	4.90–15.64	3.38–17.31	3.47–25.93	4.24–10.33	3.38–25.93
Age at exam							
Mean	4.96	15.64	7.92	10.76	18.31	9.66	
s.e.	0.37	0.42	0.45	4.86	0.48	0.35	
Median	5.01	15.22	7.77	6.15	18.53	9.73	
Range	3.29–7.12	5.83–25.48	4.67–15.31	5.43–25.31	8.90–26.98	6.78–13.29	
Gender							
Female	5	29	13	2	33	12	47
Male	5	28	19	2	40	10	52
Race							
White	6	46	21	2	57	14	73
Black	2	7	6	2	9	4	15
Other	2	4	5	0	7	4	11
Status							
Normal teeth	6	19	18	2	13	5	
Abnormal teeth	4	38	14	2	60	17	

compared with 77.3% (17/22) (Tables 1 and 2). No change was seen in the frequency of abnormalities in primary teeth after BMT (Table 3). In the group of patients who had full permanent dentition both before and after BMT ($N=55$), we found no change in the frequency of any abnormality after BMT ($P>0.05$; Tables 4 and 5).

We found no significant correlation between TBI and the development of dental abnormalities (Table 5). Though caries was the most frequent abnormality identified in this series, we found that, of those who had received TBI, the proportion of patients who developed caries was similar pre- and post-BMT.

Among 73 patients who had adult teeth after BMT, 32 (44%) patients had caries. Of these 32 patients who had caries, three patients had grade 1 acute GVHD and nine patients had chronic GVHD. Among 55 patients who had adult teeth both before BMT and after BMT, 27 (49%) had caries. Of these 27 patients who had caries, three had grade 1 acute GVHD, and six had chronic GVHD. Among 32 of the 73 (44%) patients with adult teeth after BMT who had

Table 2 Frequency of abnormalities in patients who had mixed dentition before ($N=32$) or after ($N=22$) BMT

Type of abnormality	*Number of patients (%)*	
	Before BMT (N=32)	*After BMT (N=22)*
Enamel pearl	3 (9.4%)	4 (18.2%)
Caries	10 (31.3%)	7 (31.8%)
Extraction	3 (9.4%)	3 (13.6%)
Pulp calcification	1 (3.1%)	1 (4.5%)
Root stunting	0	8 (36.4%)
Hypodontia	1 (3.1%)	1 (4.5%)
Taurodontia	2 (6.3%)	1 (4.5%)

Table 3 Frequency of abnormalities in patients who had primary teeth before ($N=10$) or after ($N=4$) BMT

Type of abnormality	*Number of patients*	
	Before BMT (N=10)	*After BMT (N=4)*
Enamel pearl	1 (10.0%)	0
Caries	3 (30.0%)	1 (25.0%)
Hypodontia	0	1 (25.0%)
Extraction	0	1 (25.0%)
Taurodontia	1 (10.0%)	0

Table 5 Frequency of abnormalities in patients who had permanent teeth both before and after BMT ($N=55$)

Type of abnormality	*Number of patients with permanent dentition*	
	Before BMT (N=55)	*After BMT (N=55)*
Enamel pearl	1 (1.8%)	1 (1.8%)
Caries	24 (43.6%)	27 (49.1%)
Extraction	10 (18.2%)	19 (34.5%)
Pulp calcification	4 (7.3%)	12 (21.8%)
Root stunting	3 (5.5%)	7 (12.7%)
Hypodontia	1 (1.8%)	1 (1.8%)
Microdontia	3 (5.5%)	4 (7.3%)
Taurodontia	3 (5.5%)	3 (5.5%)

Table 4 Demographic information and general dental status (normal *vs* abnormal) of patients who had permanent dentition both pre- and post-BMT by normality type

Patient characteristics	*Before BMT*		*After BMT*		*Total (N=55)*
	Abnormal (N=37)	*Normal (N=18)*	*Abnormal (N=44)*	*Normal (N=11)*	
Age at BMT					
Mean	16.53	15.36	16.34	14.89	16.15
s.e.	0.49	0.75	0.47	0.95	0.41
Median	15.76	14.97	15.81	14.19	15.56
Range	12.05–25.93	11.16–21.34	8.23–25.93	11.16–19.99	11.16–25.93
Age at exam					
Mean	16.17	15.00	19.99	18.01	
s.e.	0.46	0.73	0.54	0.80	
Median	15.51	14.40	19.26	17.29	
Range	11.76–25.48	11.08–21.30	11.21–26.98	14.48–21.45	
Gender					
Female	19	9	21	7	28
Male	18	9	23	4	27
Race					
White	29	16	35	10	45
Black	6	1	7	0	7
Other	2	1	2	1	3
TBI					
No	6	4	8	2	10
Not assigned	0	1	0	1	1
Yes	31	13	36	8	44

caries post-BMT, nine also had root stunting, three had microdontia, and one had taurodontia.

Discussion

We found that nearly 60% of pediatric patients had dental abnormalities on pre-BMT dental radiographs. Not unexpectedly, abnormalities were identified in an even greater number of patients (80%) post-BMT. Those who underwent BMT with mixed dentition had the greatest increase in dental abnormalities. Such a finding can be explained by the effect of therapeutic insults on rapid odontogenic changes that occur during the period of mixed dentition. These developmental changes ultimately manifest as abnormalities of permanent dentition. In contrast, patients with permanent dentition entering BMT preparation would be expected to maintain pre-existing dental abnormalities or complete the abnormal development induced prior to BMT. Such was the case in this study where the frequency of dental abnormalities did not change between pre-BMT and post-BMT imaging, but the frequency of root stunting increased in those who transitioned between mixed and permanent dentition.

Many of the chemotherapy agents used to treat childhood malignancies disrupt tooth formation.[18,19] The known long-term effects associated with chemotherapy include tooth agenesis, microdontia, root stunting, enamel hypoplasia, and alteration of facial growth. Previous reports have observed treatment-related hypodontia, microdontia, enamel hypoplasia, root stunting, taurodontia, over-retention of primary teeth, and an increased caries index in survivors of childhood cancer.[10–13] Impaired root development decreases the growth of alveolar bone, thus impairing the vertical development of the mandible and the lower third of the face.[14] Other reported adverse sequelae include malocclusion,[15] narrowing of the pulp canal,[16] and reduced temporomandibular joint mobility.[17]

Alteration of odontogenesis by chemotherapy or radiation can result in hypodontia. The conditioning therapy given before BMT to eliminate residual malignant cells or defective stem cells and prevent GVHD involves high doses of chemotherapy and/or TBI, and can contribute to altered dental development. However, hypodontia is a common occurrence in the healthy population, with a reported incidence of 35%.[11] When third molars are excluded, hypodontia rates of 2.2–10.1% have been reported; the maxillary lateral incisor and mandibular second premolar are the teeth most commonly affected.[20–23] Other dental abnormalities observed in this study often occur in the general population as a result of genetic inheritance or as part of a syndrome. The frequency of microdontia, taurodontia, and enamel pearls differed little from the norms for a healthy population. Therefore, these four dental anomalies may not be treatment-related sequelae in the studied population.

The results of this study indicate that children who undergo BMT experience a wide range of dental abnormalities, many of which exist prior to BMT. However, in this cohort, an increase in root stunting among patients in transition from primary to permanent teeth was the only statistically significant finding, with 5% of these patients exhibiting root stunting before BMT compared to 27% after BMT. The initial insult-prompting root stunting likely predated the BMT. Prospective longitudinal studies will be needed to fully answer this question.

Our finding of approximately one-third of patients with permanent dentition who also have GVHD following BMT supports prior reports of an increased risk of dental caries after BMT.[10–13] However, we found no significant increase in the frequency of caries or in dental restorations and extractions, which serve as an indicator of the progression of caries, when comparing the frequency of caries in those patients evaluated prior to and after BMT. We further found no significant association between treatment with TBI and caries. Radiation of 1000 cGy or more may result in reduced salivary flow, leading to an altered pH balance in the oral cavity, causing a shift in oral flora and an increase in caries.[2,11] Dietary factors, such as a high-carbohydrate diet and difficulty with oral hygiene because of mucositis may also contribute to the risk of caries.[11] A decrease in the elasticity of the perioral tissues has also been noted in patients after BMT, which may also increase the risk of dental complications by reducing access to the oral cavity.[2,24] Berkowitz[25] noted histopathologic changes in the minor salivary glands and resultant xerostomia in all patients in his study who had chronic GVHD. Other researchers have also noted xerostomia after BMT,[2,26–28] and this effect has been linked to an increase in the incidence of dental caries.

We found a trend toward increased frequency of pulpal calcification after BMT, although no statistically significant effect was observed. Pulpal calcification may not be a sequela of treatment: al-Hadi Hamasha[29] has reported a prevalence rate of 22% in a healthy population. However, the excess frequency of caries and pulpal calcification detected in this study warrants further investigation.

Conclusion

Although previous research has shown children to be at increased risk of caries, hypodontia, microdontia, taurodontia, and pulpal calcification after BMT, the results of this study corroborated the previous data only in the case of root stunting. The median age of this cohort at the time of BMT (13.5 years) reflects a population primarily composed of patients who had or would soon have complete permanent dentition and who thus had already experienced the maximal insult to odontogenesis. Further increases in dental abnormalities other than caries would therefore be unlikely. However, patients who had not reached dental maturation at the time of BMT demonstrated an increase in root stunting after BMT. The patients' primary treatment is likely to be implicated in the high frequency of dental abnormalities observed before BMT, and is supported by the high frequency of abnormalities seen in these patients on pre-BMT examinations and panoramic radiography. Previous studies of the long-term dental consequences of BMT have focused on younger age groups[11,12] and therefore have observed a greater frequency of abnormalities, as would be expected when odontogenesis is impaired at an earlier stage.

The current study underscores the frequency of caries in this survivor population at risk for dental toxicity. Routine dental evaluation and meticulous dental hygiene are needed not only during the pre-transplant period but also should be continued long-term.

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