ORTHODONTICS & CRANIOFACIAL RESEARCH

ORIGINAL ARTICLE

M. Vesterbacka
O. Ringdén
M. Remberger
J. Huggare
G. Dahllöf

Disturbances in dental development and craniofacial growth in children treated with hematopoietic stem cell transplantation

Authors' affiliations:
M. Vesterbacka, J. Huggare, G. Dahllöf, Division of Orthodontics and Pediatric Dentistry, Department of Dental Medicine, Karolinska Institutet, Stockholm, Sweden
O. Ringdén, M. Remberger, Center for Allogeneic Stem Cell Transplantation, Karolinska Institutet, Karolinska University Hospital at Huddinge, Stockholm, Sweden

Correspondence to:
Prof Göran Dahllöf
Division of Orthodontics and Pediatric Dentistry
Department of Dental Medicine
Karolinska Institutet
POB 4064
SE-141 04 Huddinge
Sweden
E-mail: Goran.Dahllof@ki.se

Date:
Accepted 12 November 2011

DOI: 10.1111/j.1601-6343.2011.01533.x

Vesterbacka M., Ringdén O., Remberger M., Huggare J., Dahllöf G. Disturbances in dental development and craniofacial growth in children treated with hematopoietic stem cell transplantation.
Orthod Craniofac Res 2012;**15**:21–29 © John Wiley & Sons A/S

Structured Abstract

Objectives – To investigate the correlation between age, degree of disturbances in dental development, and vertical growth of the face in children treated with hematopoietic stem cell transplantation (HSCT).

Patients – 39 long-term survivors of HSCT performed in childhood and transplanted before the age of 12, at a mean age of 6.8 ± 3.3 years.

Methods – Panoramic and cephalometric radiographs were taken at a mean age of 16.2 years. For each patient two age- and sex-matched healthy controls were included. The area of three mandibular teeth was measured and a cephalometric analysis was performed.

Results – The mean area of the mandibular central incisor, first and second molar was significantly smaller in the HSCT group, and the vertical growth of the face was significantly reduced, especially in the lower third, compared to healthy controls. A statistically significant correlation between age at HSCT, degree of disturbances in dental development, and vertical growth of the face was found. Children subjected to pre-HSCT chemotherapy protocols had significantly more growth reduction in vertical craniofacial variables compared to children without pre-HSCT chemotherapy. Conditioning regimens including busulfan or total body irradiation had similar deleterious effects on tooth area reduction and craniofacial parameters.

Conclusions – The younger the child is at HSCT, the greater the impairment in dental and vertical facial development. This supports the suggestion that the reduction in lower facial height found in SCT children mainly is a result of impaired dental development and that young age is a risk factor for more severe disturbances.

Key words: children; craniofacial growth; dental development; late adverse effects; stem cell transplantation

Introduction

The improved survival rates of children diagnosed with cancer are attributed to the use of cancer treatments combining surgery, multiagent chemotherapy and radiotherapy in addition to improved supportive care. Currently, the 5-year survival rate for acute lymphoblastic leukemia, the most common cancer in childhood, exceeds 80% (1). Approximately, two-thirds of the survivors of childhood cancer will develop at least one chronic or late-occurring complication or disability that can be attributed to previous cancer treatment (2). In children treated with hematopoietic stem cell transplantation (HSCT), as many as 93% had one or more adverse sequelae reported. Late effects are often not life-threatening but significantly impair quality of life of long-term survivors and include chronic graft-versus-host disease, endocrine, pulmonary, ocular, and dental disturbances (3).

Following HSCT in childhood long-term complications of the oral and craniofacial complex is frequent. Decreased salivary function, increased risk of caries, oral infections, increased incidence of temporomandibular dysfunction, disturbances in dental development (4), and decreased craniofacial growth have been reported (5–7). Agenesis, microdontia, disturbances in root formation resulting in thin, short V-shaped roots with premature apical closure are commonly encountered in survivors of HSCT performed in childhood (8–10). Tooth size reduction is evident in the majority of children treated with HSCT, with the most pronounced effect seen in the formation of the roots. Total body irradiation (TBI) seems to have a more detrimental effect on the tooth germ compared to chemotherapy alone (11, 12).

Hematopoietic stem cell transplantation in childhood including conditioning with TBI has been shown to impair linear growth, by inducing neuroendocrine deficiency and by direct toxicity to the bone epiphysis (3, 13). TBI preparative regimens have also been shown to impair the growth of the craniofacial complex (14, 15). Vertical development of the face and in particular in the lower third is intimately associated with the growth of the alveolar bone. The alveolar bone grows in response to the formation and eruption of teeth (16), and an impaired dental development will thus result in a reduction in alveolar vertical growth (15). The hypothesis to be tested in this study is that the younger the age at HSCT, the more severe dental developmental disturbances and the more deficient vertical growth of the lower face height will be found.

Patients and methods

Patients

This study included 39 recipients of allogeneic HSCT, performed at Huddinge Hospital between 1980 and 1998. The majority was treated for a hematological malignancy, but non-malignant diagnosis, such as severe aplastic anemia (SAA) and metabolic diseases were also found. As conditioning treatment, most children received high-dose cyclophosphamide (Cy) (total dose of 120 mg/kg) in combination with 10 Gy TBI in a single dose. Others received Cy in combination with busulfan (Bu) (4 mg/kg p.o in divided dosed daily for 4 days). Some of the patients with a non-malignant diagnosis had either a lower dose of TBI or an addition (to Cy/TBI or Bu/Cy) of another cytostatic drug (16). As prophylaxis against graft-versus-host disease (GVHD), methotrexate, cyclosporine A, or a combination of these was given to all children (17, 18). Baseline characteristics for the patient group are outlined in Table 1.

These 39 subjects included had been treated with HSCT at an age of 12 years or younger, had survived for at least 3 years, and had a cephalometric and a panoramic radiograph (PRG) of good quality taken when the patient was at least 12 years of age and taken at least 3 years after the transplantation.

For each patient, two healthy controls matched for age (mean; 16.2 ± 2.4 years) and gender were selected from the patient files at the Department of Orthodontics. Only those with a moderate degree of malocclusion and those having a good quality PRG and cephalogram taken before orthodontic treatment were selected. The local

Table 1. **Baseline characteristics of hematopoietic stem cell recipients**

Variables	
Number of patients	39
Male/Female	20/19
Age at BMT (years)	
Mean	6.8 ± 3.3
Range	1.5–12.4
Age at follow-up (years)	
Mean	16.2 ± 2.4
Range	12.2–20.2
Follow-up time (years)	
Mean (years)	9.4
Diagnosis (numbers)	
Acute lymphoblastic leukaemia	14
Acute myeloid leukaemia	8
Aplastic anaemia	2
Metabolic disease	12
Chronic lymphoproliferative disease	1
Lymphoma	1
Myelodysplastic syndrome	1
Remission (children with malignant diseases)	
First	11
Second	8
Third to ninth	5
Donor type	
HLA identical sibling/related	33
Matched unrelated donor	3
Mismatched	3
Conditioning	
Cy + TBI	22
Cy + TBI 8	3
Cy + TBI + Flud	1
Bu + Cy	11
Bu + Cy + VP16	2
Graft-versus-host disease prophylaxis	
Mtx + CsA	22
CsA	11
Mtx	6
Growth hormone treatment (number of patients)	
Yes	26
No	13

Cy, cyclophosphamide; TBI, total body irradiation; Bu, busulphan; VP16, etopside; Flud, fludarabine; Mtx, methotrexate; CsA, cyclosporine A.

ethical committee at Karolinska University Hospital, Huddinge, approved the protocol for this study.

Methods

A panoramic radiograph of the teeth and a lateral cephalometric radiograph were taken of all children in connection with dental examination (patients) or orthodontic treatment planning (controls), at the Department of Dental Medicine, Karolinska Institutet. The degree of dental developmental disturbances was evaluated by measuring the area of the mandibular left central incisor, first and second molar on the PRG. If the outline of any of the teeth was difficult to trace, the contra lateral tooth was measured instead. One of the authors (MV) made the measurements of tooth areas (crown and root), using a manual planimetric instrument (OTT-Planimeter/A.Ott Kempten Bayern), with an accuracy of 0.02 cm^2 (19). Each tooth was measured twice and the mean was registered (12).

The enlargement factor incorporated in panoramic radiographs is difficult to control as it varies in different areas of the picture and between individuals. It is reasonable to assume, however, that these variations are randomly distributed, and under such circumstances, the enlargement error should not affect comparisons of mean values to any mentionable degree. This assumption has been tested and confirmed by Näsman et al. (12) in an earlier study.

The cephalograms were exposed according to a standard method and analyzed by one author (MV). The craniofacial variables evaluated were based on the cephalometric reference points and lines earlier described by Dahllöf et al. (20). All measurements were made with an electronic digitizer on-line with a microcomputer. The resolution of the instrument was 0.1 mm and 0.1°. As different cephalostats were used, all linear measurements were corrected for magnification.

To test the reliability of the method, duplicate measurements were made on the cephalograms of 19 randomly selected subjects. The error of the method (S_i) was calculated using the formula: $S_i = \sqrt{(\sum d^2/2N)}$. where d is the difference between two measurements, and N is the number of double determinations. The error was found to vary between 0.07 mm (id-ML) and 1.76 mm (cd-pgn)

for the linear measurements and between 0.11° (ML/NL) and 0.39° (SNA) for the angular measures.

For comparison of mean values and standard deviations, unpaired t-tests were used. Linear regression analyses were performed for the correlation of the variables age at HSCT, mean tooth area, and alveolar height.

Results

The results of this study show that both dental development and craniofacial growth are impaired in children treated with allogeneic HSCT before the age of 12 years and that there exists a correlation between age at HSCT, degree of disturbances to dental developmental, growth of the alveolar processes, and the vertical growth of the face.

For all three teeth analyzed (the mandibular left central incisor, first and second molar), the mean area was significantly reduced in the HSCT group compared to the control group. The mean difference in size of the first molar, between the groups, was about 0.5 cm^2 and even larger (0.9 cm^2) for the second molar (Table 2).

A significant correlation between age at HSCT and mean tooth area was found ($p < 0.001$), as can be seen in Fig. 1, for the lower first permanent molar. The same correlation was found for the other teeth examined as well. The older the child was at HSCT, the fewer disturbances in tooth development were seen.

Table 2. **Mean tooth areas of mandibular teeth obtained from panoramic radiographs in hematopoietic stem cell transplantation (HSCT) group and control group: comparison of mean values**

	HSCT group (n = 39)	Control group (n = 78)	
Tooth	Mean (SD) (cm^2)	Mean (SD) (cm^2)	Significance *p*-value[†]
Lower central incisor	0.751 (0.156)	0.975 (0.137)	<0.001
Lower first molar	2.352 (0.362)	2.874 (0.364)	<0.001
Lower second molar[‡]	1.930 (0.518)	2.835 (0.343)	<0.001

[†]Student's *t*-test.
[‡]HSCT n = 36, because of aplasia.

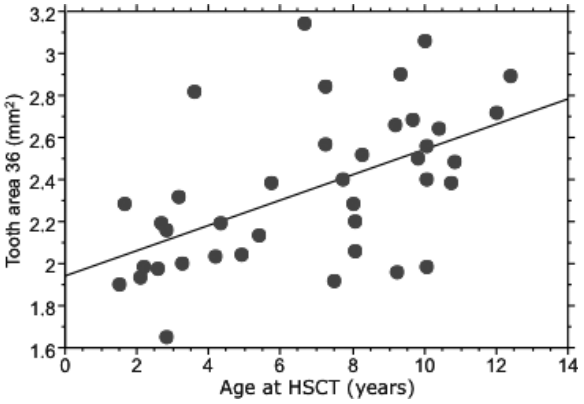

Fig. 1. Correlation between age at hematopoietic stem cell transplantation (HSCT) and mean area of the lower left first molar (Area 36) in HSCT children.

No significant differences were found in tooth area between 13 adolescents conditioned with Bu in combination with Cy compared to 26 conditioned with Cy/TBI. The mandibular length was longer in Bu/Cy-treated children, but the difference did not reach statistical significance. On the other hand, the height of the mandibular alveolar process was significantly higher in Bu/Cy-treated children compared to Cy/TBI, both anteriorly (id-ML) ($p < 0.05$) and posteriorly (Lj6-ML) ($p < 0.05$).

Acute GVHD grades II–IV were diagnosed in three of the 39 patients and chronic GVHD in nine patients. Within the HSCT group, there were no significant differences between those diagnosed with aGVHD or cGVHD and those not, with regard to tooth area or vertical and linear dimensions of the face.

When analyzing the vertical growth of the face, all linear vertical measures, except for upper anterior facial height (n-ans), were significantly diminished in the HSCT group compared to the control group (Table 3). The mean difference in total facial height (n-gn), between the groups, was more than that 4 mm, and this difference was mainly due to a reduction in the lower facial height (mean diff; 4.5 mm, $p < 0.002$). A statistically significant difference, between the groups, was seen in the height of the alveolar processes, ranging from 1.3 mm ($p < 0.018$) in the region of the lower first molar (Lj6-ML) to 1.9 mm ($p < 0.001$) for the upper posterior alveolar height (Uj6-NL).

Table 3. **Comparison of vertical cephalometric measures, obtained from analyses of lateral radiographs, between hematopoietic stem cell transplantation (HSCT) group and control group**

Variables[†]	HSCT group (n = 39) Mean (SD) (mm)	Control group (n = 78) Mean (SD) (mm)	Significance *p*-value[‡]
n-gn	108.0 (7.4)	112.2 (6.3)	0.002
n-ans	48.2 (3.2)	48.6 (2.5)	0.563
se-pns	42.7 (3.6)	45.5 (3.3)	<0.001
ans-gn	57.5 (5.1)	62.0 (5.0)	<0.001
pr-NL	14.1 (2.4)	15.4 (2.3)	0.004
Uj6-NL	20.7 (2.4)	22.6 (2.5)	<0.001
Uj7-NL[§]	18.3 (2.2)	20.0 (2.6)	<0.001
id-ML	26.6 (2.6)	28.5 (2.4)	<0.001
Lj6-ML	29.2 (2.6)	30.5 (2.7)	0.018
Lj7-ML[¶]	27.4 (2.2)	29.3 (2.7)	<0.001

[†]n-gn, anterior facial height; n-ans, upper anterior facial height; se-pns, upper posterior facial height; ans-gn, lower anterior facial height; pr-NL, upper anterior alveolar height (in upper incisor region); Uj6-NL, upper posterior alveolar height (in first molar region); Uj7-NL, upper posterior alveolar height; (in second molar region); id-ML, lower anterior alveolar height (in lower incisor region); Lj6-ML, lower posterior alveolar height (in first molar region) Lj7-ML, lower posterior alveolar height (in second molar region).
[‡]Student's *t*-test.
[§]HSCT n = 36. Control n = 69. Because of aplasia or not fully erupted teeth.
[¶]HCST n = 36. Control n = 72. Because of aplasia or not fully erupted teeth.

Table 4. **Comparison of vertical cephalometric measures, obtained from analyses of lateral radiographs, between children subjected to chemotherapy protocols prior to HSCT and those not**

Variables[†]	Pre-HSCT chemotherapy (n = 24) Mean (SD) (mm)	No prior chemotherapy (n = 15) Mean (SD) (mm)	Significance *p*-value[‡]
n-gn	105.60 (6.6)	111.8 (7.0)	0.008
n-ans	47.7 (3.1)	49.1 (3.4)	0.224
se-pns	41.6 (2.9)	44.6 (3.9)	0.009
ans-gn	56.0 (5.2)	59.9 (4.2)	0.019
pr-NL	13.4 (2.6)	15.3 (1.7)	0.016
Uj6-NL	20.1 (2.3)	21.7 (2.2)	0.031
Uj7-NL[§]	18.0 (2.2)	18.7 (2.3)	0.321
id-ML	25.8 (2.7)	27.9 (1.9)	0.013
Lj6-ML	28.5 (2.6)	30.3 (2.3)	0.034
Lj7-ML[§]	26.9 (2.4)	28.2 (1.8)	0.085

[†]n-gn, anterior facial height; n-ans, upper anterior facial height; se-pns, upper posterior facial height; ans-gn, lower anterior facial height pr-NL, upper anterior alveolar height (in upper incisor region); Uj6-NL, upper posterior alveolar height (in first molar region); Uj7-NL= upper posterior alveolar height (in second molar region); id-ML, lower anterior alveolar height (in lower incisor region); Lj6-ML, lower posterior alveolar height (in first molar region); Lj7-ML, lower posterior alveolar height (in second molar region).
[‡]Student's *t*-test.
[§]Pre-HSCT chemotherapy group (n = 21). Because of aplasia or not fully erupted teeth.

When considering the length of the anterior cranial base and the maxillary length, no significant difference was seen between the groups. The length of the mandible was significantly diminished (mean difference; 5.5 mm, $p < 0.001$) in the HSCT group. The anterio-posterior position (SNA, SNB) and the vertical inclination (ML/NSL, ML/NL) of the mandible and maxilla were not influenced by HSCT, with the exception of the inclination of the maxilla (NL/NSL), which was slightly increased in the HSCT group (mean difference; 1.7°, $p < 0.01$).

In the HSCT group, 24 children were treated because of malignant diseases and had all been subjected to pre-HSCT chemotherapy protocols. As can be seen in Table 1, 11 children were in first remission, eight children in second remission, and five children in third or later remissions. Children subjected to pre-HSCT chemotherapy exhibited significantly reduced growth of all vertical dimensions except upper anterior facial height (Table 4), but we found no differences in tooth areas between the two groups.

A statistically significant correlation between age and the measures of alveolar height, Uj6-NL ($p < 0.01$) and Lj6-ML ($p < 0.05$) were found, with more pronounced disturbances in alveolar bone growth in those treated with HSCT at a young age. For the other values describing alveolar height, an association between age and growth was also seen, but without reaching the level of significance.

The correlation between dental disturbances and vertical growth of the face was also analyzed by plotting the area of the three mandibular teeth against the alveolar height in the corresponding

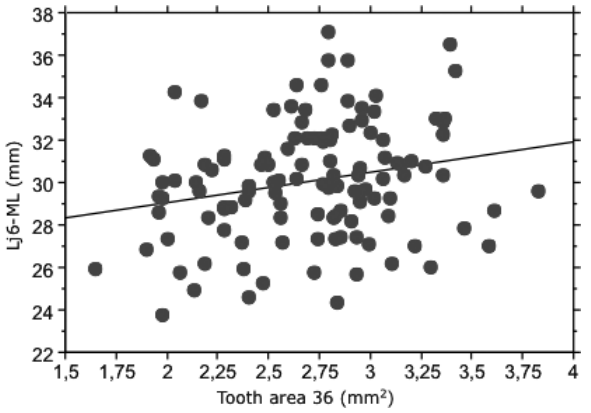

Fig. 2. Correlation between mean area of the first lower molar and the mean alveolar height in that region (Lj6-ML) in hematopoietic stem cell transplantation children.

region. A statistically significant correlation ($p < 0.01$) was found between tooth area of the first lower molar and the alveolar height in that region, shown in Fig. 2.

Finally, three multiple regression analyses were performed, to test the correlation between the age at HSCT, the degree of dental developmental disturbances, and the vertical growth of the alveolar processes. The results show that there are statistically significant correlations between the age at HSCT, tooth area, and alveolar height ($p < 0.01$). The younger the child is at HSCT, the greater the impairment in dental and then also in vertical facial development. The regression analyses for the investigated teeth are shown in Fig. 3A–C.

Discussion

The results of this study show two novel findings with regard to the effects of chemotherapy and

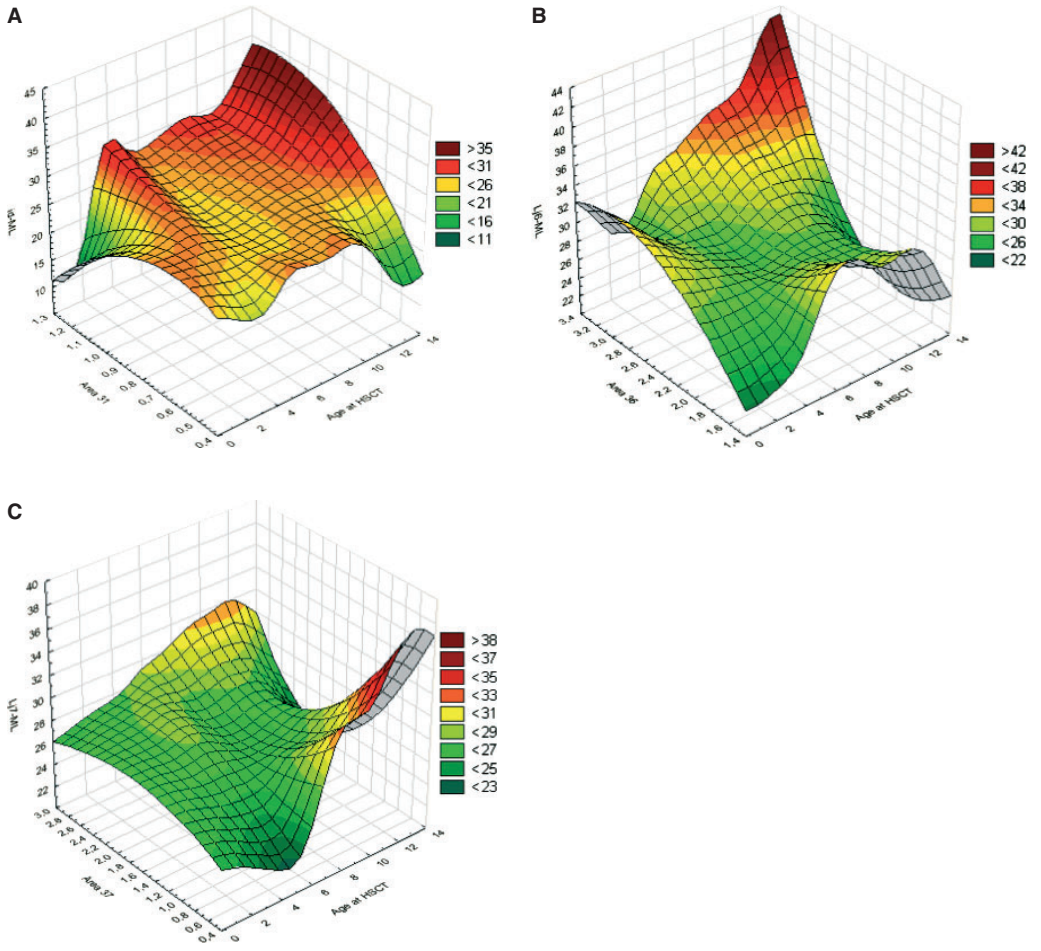

Fig. 3. Linear regression analysis correlating age at hematopoietic stem cell transplantation (HSCT) with (A) mean area of the first left lower central incisor (31) and alveolar height in that region (id-ML) in HSCT children. (B) Linear regression analysis correlating age at HSCT with mean area of the first left lower molar (36) and the alveolar height in that region (Lj6-ML) in HSCT children. (C) Linear regression analysis correlating age at HSCT with mean area of the first left lower second molar (37) and alveolar height in that region (Lj7-ML) in HSCT children.

radiation therapy on dental and craniofacial growth. Firstly, it was shown that busulfan is as deleterious as single-dose TBI with regard to dental development and craniofacial growth and, secondly, that there is a strong correlation between age at HSCT, degree of disturbances to dental development, and the vertical growth of the face.

In this study, 39 children treated with hematopoietic stem cell transplantation before the age of 12 were examined after 9 years, at a mean age of 16 years, at a time when all permanent teeth, except third molars should be erupted and in occlusion. The majority of the patients had received TBI/Cy as conditioning regimes, but about one-third had received Bu/Cy before transplantation. Both TBI/Cy and Bu/Cy cause long-term side effects. Interstitial pneumonitis, cataract, and growth retardation are some of the potential toxic effects of TBI/Cy. When using Bu/Cy, these side effects can possibly be reduced, but on the other hand, Bu/Cy has some disadvantages. It has some toxic effects that are rarer using TBI/Cy, such as permanent alopecia, hemorrhagic cystitis, and veno-occlusive disease of the liver (21). According to Ferry and Socie (22), endocrinological disturbances are frequent after TBI/Cy, but results are less definitive after a Bu/Cy-based conditioning regimen. Their result also shows that growth impairment is well established after TBI including regimens. This is confirmed in the analysis by Cohen et al. (23), which also suggest that Bu/Cy conditioning regimen has less interference with the growth process than irradiation. We have previously shown that salivary dysfunction induced by Bu is correlated with the total systemic exposure of Bu (24). In this study, most parameters studied in those conditioned with Bu/Cy were similar to those conditioned with TBI/Cy, except for variables describing mandibular alveolar height. This may indicate that Bu/Cy does not have an equally deleterious effect on the enchondral bone formation in the mandible as TBI/Cy. Even though the results of this study show that Bu/Cy is equally deleterious to dental development and craniofacial growth as is single-dose TBI combined with Cy.

Concerning the effect of HSCT on tooth development, we found significantly reduced tooth areas in the HSCT group compared to the control group and this was in agreement with earlier studies (11, 25). A significant correlation between age at HSCT and tooth size was seen, indicating a more detrimental effect on tooth development in those treated with HSCT at a young age. Other studies have also reported the negative influence of young age and suggested that young age at HSCT was a stronger risk factor for severe dental impairment than TBI (10, 11). Also in children treated with chemotherapy protocols, disturbances in dental development were significantly more frequent in children treated before 5 years of age compared to older children (26).

We also found significantly diminished linear craniofacial measures in adolescents treated with HSCT in accordance with earlier studies (7, 20, 27). For the length of the anterior cranial base and the maxilla, no significant differences compared to the controls were seen, probably reflecting the early completion of growth of the anterior cranial base and the lack of endochondral bone formation of the maxilla (15). In comparison with the maxilla, the length of the mandible was significantly reduced in the HSCT group. This is in accordance with earlier reports; we (20) reported the negative effect on mandibular growth to be four times as great as for the maxilla, reflecting the radiosensitivity of dividing cells in the condylar cartilage, resulting in decreased growth of the condyle. Our findings are also in line with Karsila-Tenovuo et al. (28) who reported significant vertical growth impairment in children with solid intracranial tumors, when the treatment regimen included cranial irradiation.

The vertical growth of the face was significantly reduced in those treated with HSCT. The only vertical variable not statistically different between the groups was the upper anterior facial height. As the upper posterior facial height was reduced in the HSCT group, a slight posterior inclination of the maxilla was found, evidenced by a minor increase in the angle NL/NSL compared to controls. Dahllöf et al. (20) reported a similar difference in maxillary inclination. This increase in the inclination of the maxilla was the only positional change found of the jaws, as neither the anterioposterior position of the jaws nor the vertical

inclination of the mandible seemed to be influenced by the HSCT, and this was also in accordance with earlier findings. The reduction in total facial height was almost totally a result of the decrease in growth of the lower third of the face, with significantly reduced height of the alveolar processes, implicating an association between tooth eruption and alveolar bone growth (14, 20). We also found that craniofacial growth was further diminished if children had been subjected to pre-HSCT chemotherapy protocols. Children who have received chemotherapy or particularly cranial irradiation prior to HSCT and conditioned with TBI develop a growth hormone deficiency resulting in growth impairment (29, 30).

When correlating the age at HSCT with growth of the alveolar processes, statistically significant correlations were seen in the upper and lower first molar regions, with less disturbances in vertical growth found in children treated at an older age. Multiple regression analyses were performed for the variables age at HSCT, tooth area, and alveolar height. The results of these analyses showed a significant correlation between these factors, supporting the hypothesis that the younger the age at HSCT, the more severe dental developmental disturbances and the more deficient vertical growth of the lower face will be found.

It is known that eruption of teeth is important for the development of the alveolar processes and vertical growth of the face (16), and this study supports the earlier suggestion (14) that the reduction in lower facial height found in HSCT children mainly is a result of impaired dental development and that young age is a risk factor for more severe dental disturbances.

Graft-versus-host disease may be associated with growth impairment because of the growth suppressive effects of glucocorticoids. In this study, nine patients were diagnosed with cGVHD. It has been reported that once cGVHD is controlled, growth rates may return to normal (31).

Orthodontic treatment did not produce any major harmful side effects, even though most of the patients exhibited severe disturbances in dental development, in ten adolescents, all long-term survivors after HSCT (32). One of these 10 patients showed evidence of root resorption. It seems that the short roots in these patients do not predispose them to an increased risk of root resorption during active treatment. Ideal treatment results were not always achieved. The treatment result was judged unsatisfactory in four of ten patients because of factors such as finished pubertal growth spurt or treatment fatigue.

This study further underlines the negative effects induced by conditioning regimens in HSCT on dental and craniofacial development, effects that might influence present and future occlusion, temporomandibular function, dental and periodontal health, and in that way the quality of life. With the introduction of reduced intensity conditioning in HSCT, the reported side effects on dental development and craniofacial growth are expected to be reduced in the future.

Acknowledgements: The study was supported by grants from the Swedish Dental Society, Swedish Medical Society, Swedish Childhood Cancer Foundation and Karolinska Institutet.

References

1. Marinotto AB, Rowland JH, Yabroff KR, Scoppa S, Hachey M, Ries L et al. Long-term survivors of childhood cancers in the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18:1033–40.
2. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT et al. Chronic health conditions in adult surviviors of childhood cancer. *N Engl J Med* 2006;355:1572–82.
3. Socié G, Salooja N, Cohen A, Rovelli A, Carreras E, Locasciulli A et al. Late Effects Working Party of the European Study Group for Blood and Marrow Transplantation. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood* 2003;101:3373–85.
4. van der Pas-van Voskuilen IGM, Veerkamp JSJ, Raber-Durlacher JE, Bresters D, van Wijk, Barasch A et al. Long-term adverse effects of hematopoietic stem cell transplantation on dental development in children. *Support Care Cancer* 2009;17:1169–75.
5. Dahllöf G, Forsberg CM, Borgström B. Changes in craniofacial development induced by growth hormone therapy in children treated with bone marrow transplantation. *Acta Pediatr* 1994;83:1165–9.
6. Dahllöf G, Bågesund M, Ringdén O. Impact of conditioning regimens on salivary function, caries-associated microorganisms and dental caries in children after bone marrow trans-

plantation. A 4-year longitudinal study. *Bone Marrow Transplant* 1997;20:479–83.
7. Dahllöf G. Craniofacial growth in children treated for malignant diseases. *Acta Odontol Scand* 1998;56:378–82.
8. Pajari U, Lahtela P, Lanning M, Larmas M. Effect of anti-neoplastic therapy on dental maturity and tooth development. *J Pedod* 1988;12:266–74.
9. Dahllöf G, Barr M, Bolme P, Modeer T, Lönnqvist B, Ringdén O et al. Disturbances in dental development after total body irradiation in bone marrow transplant recipients. *Oral Surg Oral Med Oral Pathol* 1988;65:41–4.
10. Kaste SC, Goodman P, Leisenring W, Stovall M, Hayashi RJ, Yeazel M et al. Impact of radiation and chemotherapy on risk of dental abnormalities. A report from the childhood cancer survivor study. *Cancer* 2009;115:5817–27.
11. Hölttä P, Hovi L, Saarinen-Pihkala UM, Peltola J, Alaluusua S. Disturbed root development of permanent teeth after pediatric stem cell transplantation. Dental root development after SCT. *Cancer* 2005;103:1484–93.
12. Näsman M, Forsberg CM, Dahllöf G. Long-term dental development in children after treatment for malignant disease. *Eur J Orthod* 1997;19:151–9.
13. Chemaitilly W, Sklar CA. Endocrine complications in long-term survivors of childhood cancers. *Endocr Relat Cancer* 2010;17:R141–59.
14. Dahllöf G, Näsman M, Borgström A, Modéer T, Forsberg CM, Heimdahl A et al. Effect of chemotherapy on dental maturity in children with hematological malignancies. *Pediatr Dent* 1989;11:303–6.
15. Forsberg CM, Krekmanova L, Dahllöf G. The effect of growth hormone therapy on mandibular and cranial base development in children treated with total body irradiation. *Eur J Orthod* 2002;24:285–92.
16. Proffit WR. Concepts of growth and development, Early stages of development, Later stages of development. In: *Contemporary Orthodontics*, 4th edn. Mosby Company: St. Louis, MI; 2007. pp. 127–29.
17. Ringdén O, Remberger M, Ruutu T, Nikoskelainen J, Volin L, Vindeløv L et al. Increased risk of chronic graft-versus-host disease, obstructive bronchiolitis, and alopecia with busulfan versus total body irradiation: long-term results of a randomized trial in allogeneic marrow recipients with leukemia. Nordic Bone Marrow Transplantation Group. *Blood* 1999;93:2196–201.
18. Ringdén O, Remberger M, Svenberg P, Svahn BM, Dahllöf G, Gustafsson B et al. Fludarabine-based disease-specific conditioning or conventional myeloablative conditioning in hematopoietic stem cell transplantation for treatment of non-malignant diseases. *Bone Marrow Transplant* 2007;39:383–8.
19. Linder-Aronson S. Adenoids. Their effect on mode of breathing and nasal airflow and their relationship to characteristics of the facial skeleton and the denition. A biometric, rhinomanometric and cephalometro-radiographic study on children with and without adenoids. *Acta Otolaryngol Suppl* 1970;265:1–132.
20. Dahllöf G, Forsberg CM, Ringdén O, Bolme P, Borgström B, Näsman M et al. Facial growth and morphology in long-term survivors after bone marrow transplantation. *Eur J Orthod* 1989;11:332–40.
21. Ljungman P, Hassan M, Békássy AN, Ringdén O, Öberg G. High busulfan concentrations are associated with increased transplant-related mortality in allogeneic bone marrow transplant patients. *Bone Marrow Transplant* 1997;20:909–13.
22. Ferry C, Socié G. Busulphan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol* 2003;31:1182–6.
23. Cohen A, Rovelli A, Bakker B, Uderzo C, Van Lint MT, Esperou H 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;93:4109–15.
24. Garming-Legert K, Remberger M, Ringdén O, Hassan M, Dahllöf G. Long-term salivary function after conditioning with busulfan, fractionated or single dose TBI. *Oral Dis* 2011;17:670–6.
25. Duggal MS. Root surface areas in long-term survivors of childhood cancer. *Oral Oncol* 2003;39:178–83.
26. Avsar A, Elli M, Darka Ö, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;104:781–9.
27. Sonis AL, Tarbell N, Valachovic RW, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukaemia. A comparison of treatment modalities. *Cancer* 1990;66:2645–52.
28. Karsila Tenovuo S, Jahnukainen K, Peltomäki T, Minn H, Kulmala J, Salmi TT et al. Disturbances in craniofacial morphology in children treated for solid tumors. *Oral Oncol* 2001;37:586–92.
29. Sanders J. Growth and development after hematopoietic cell transplant in children. *Bone Marrow Transplant* 2008;41:223–7.
30. Sanders JE. The impact of marrow transplant preparative regimens on subsequent growth and development. The Seattle marrow transplant team. *Semin Hematol* 1991;28:244–9.
31. Shalet SM, Brennan BMD. Growth and growth hormone status after a bone marrow transplant. *Horm Res* 2002;58(Suppl. 1):86–90.
32. Dahllöf G, Jönsson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. *Am J Orthod Dentofac Orthop* 2001;120:459–65.