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Correlation of bone age, dental age, and chronological age in survivors of childhood acute lymphoblastic leukaemia

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Background. There is little information about oncotherapy-related dental development in childhood acute lymphoblastic leukaemia (ALL).
Objective. The objective of this study was to compare bone age (BA) and dental age (DA) to chronological age (CA) in childhood ALL survivors.
Methods. We retrospectively reviewed hand–wrist and panoramic radiographs of patients treated on contemporary single institution protocols for ALL between 1991 and 2004. We recorded patient demographics, therapeutic protocol, CA, DA, and BA. The cohort was divided into three categories based on age at diagnosis (< 6 years, 6–9 years, > 9 years).
Results. Of 73 patients, 39 (53.4%) were boys; 55 (75.3%) were Caucasian. Median CA at diagnosis was 4.5 years (range: 0.1–11.0 years); time to study was 4.1 years (range: 0.3–11.4 years). BA was normal in 61 (83.6%), delayed in 10 (13.7%), and advanced in 2 (2.7%). DA was normal in 41 (56.9%), delayed in 8 (11.1%), and advanced in 23 (31.9%). Abnormal BA, abnormal DA, and discrepancy between BA and DA are not statistically significantly associated with investigated patient or treatment factors.
Conclusions. DA may be altered in 43.1% of patients treated for ALL. A large prospective study is warranted to better define our observations and to determine their impact on dental and orthodontic management.

Introduction

Delay in growth and development represents established sequelae of treatment for childhood acute lymphoblastic leukaemia (ALL)[1–9], but little information is available as to the potential effect of early age oncotherapy on dental development[10–13]. As cure rates for children with ALL approach 80%, the effects of antineoplastic treatment influences on growth and development are becoming more apparent. ALL constitutes 31% of all childhood malignancies and now represents the most common paediatric malignancy[14–18]. Thus, altered dental age (DA) would potentially impact a large number of children and adolescents, and potentially influence dental care for these patients.

Contemporary treatment for ALL comprises multi-agent chemotherapy with craniospinal irradiation currently being reserved for cases of central nervous system (CNS) involvement. Both chemotherapy and radiation therapy have been shown to adversely affect longitudinal growth and pubertal development[3–9]. Altered DA in patients treated for ALL is not surprising because of the median age at which ALL is diagnosed (4 years)[14]. The peak incidence of diagnosis of ALL between the ages of 2 and 5 years[17] corresponds to a period of active dental development, and places these children at risk for therapy-associated dental abnormalities.

Dahllöf *et al.* determined dental maturity in 44 children with haematological malignancies treated with chemotherapy. They found neither a significant difference between the CA and DA in children treated with chemotherapy nor the number of erupted permanent teeth

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compared to healthy controls. They suggested that chemotherapy given to children with haematological malignancies did not interfere with dental maturity or age of permanent teeth[18]. In contrast, Purdell-Lewis *et al*. similarly found delayed eruption in a group of 45 children treated for a variety of malignancies (23 of whom were treated for ALL)[19].

To determine the impact of ALL and contemporary therapy on DA, we compared bone age (BA), DA, and chronological age (CA) in survivors of childhood ALL. We sought to identify risk factors contributing to potential discrepancy between BA and DA in relation to age at diagnosis, gender, race, the presence or absence of radiation therapy exposure, the total dosage of radiation therapy (= or > 24 Gy), and the total dosage of prednisone-equivalent steroid dose (> or ≤ 8000 mg/m^2). Understanding of this complication of childhood oncotherapy is necessary for the timing of orthodontic care of children and adolescents at risk for altered DA.

Materials and methods

We retrospectively reviewed medical records, panoramic radiographs, and BA reports in paediatric patients previously treated for ALL at St Jude Children's Research Hospital, and who underwent routine dental evaluation and had both a panoramic dental radiograph and hand–wrist radiograph for BA determination within 24 h of each other between 1991 and 2004. The study cohort comprised children treated between July 1983 and 30 May 2004. The study was approved by the Institutional Office of Human Subjects Protection, and the review of all records was in compliance with the Health Information Portability and Accountability Act of 1996. Informed consent was waived.

Panoramic radiographs were obtained using a Siemens Orthophos 3 or SS White Orthopantomograph (Siemens, Erlanger, Germany). All panoramic radiographs were evaluated by a senior orthodontic dental resident (M. B. M.) under the supervision of a practicing paediatric dentist (C. R.). All panoramic radiographs were reviewed and scored in a blinded manner and without knowledge of patient age or race, treatment factors, or BA. DAs were determined by directly comparing the developmental appearance of left hemimandible dentition to the system of DA assessment described by Demirjian *et al*., and recorded for each panoramic radiograph[20]. This method of estimating dental maturity is based on the quantification of the stage of maturity of each tooth in the hemimandible. The individual tooth scores are added together to determine the overall maturity score of the individual patient. The patient's score is compared to the percentile chart established by Demirjian *et al*. for conversion to an overall DA[20].With this system, the dental maturity of boys and girls is coded separately. Patients whose panoramic radiograph demonstrated a DA of 12 years or greater were excluded from the study as dental development would be expected to be nearly complete.

BA, determined according to Greulich and Pyle's 1959 atlas[21], from hand–wrist radiographs had been previously determined by staff board-certified radiologists holding certificates of Added Qualifications in Pediatric Radiology. All patients had at least one panoramic and one hand–wrist radiograph, which had been obtained within 24 h of each other. For patients with multiple examinations, we used the most recent paired studies. A BA that varied from CA by more than two standard deviations from the normative mean published in Greulich and Pyle reference[8] was considered as advanced or delayed. BA interpretation was performed in a blinded manner without knowledge of panoramic radiographic information or treatment factors.

We obtained the following data for each patient from medical records: patient demographics, diagnosis date, initial examination date, treatment protocols in addition to dates of treatment, DA, and BAs from hand–wrist radiographs. We derived the relative relationship between skeletal maturation and dental development (both categorized as delayed, normal, or advanced) from BAs and panoramic radiographs, respectively.

Treatment categories

Patients were treated for ALL between 1991 and 2004 at a single institution according

to institutional review board-approved institutional total therapy protocols XIII through total therapy XV[15,16]. Although treatment varied by protocol during the nearly 15 years, all patients received vincristine, 6-mercaptopurine, methotrexate, and dexamethasone. Craniospinal irradiation was reserved for patients with CNS leukaemia.

We categorized patients for whom complete treatment history was available, based on known or expected treatment exposures to cumulative dose in mg/m^2 of body surface area in prednisone or the equivalent dose of dexamethasone ($< vs. \geq 8000\ mg/m^2$) and total dosage in Gy of craniospinal irradiation.

Statistical analysis

The patient cohort ($n = 73$) was divided into three age groups: group 1 (patients whose ages at diagnosis were < 6 years, group 2 (patients whose ages at diagnosis were 6–9 years) and group 3 (patients whose ages at diagnosis were > 9 years). These categories were based on the estimated stages of dental maturity at the time of diagnosis (i.e., group 1, primary dentition; group 2, mixed dentition; and group 3, mixed to early mature dentition). We used the method of Clopper and Pearson[22] to obtain 95% exact confidence intervals (CI) for the proportions of BA delay, DA delay, BA abnormality, DA abnormality (with abnormality comprising advanced and delayed BA and DA), and abnormal discrepancy between BA and DA for each age group. A discrepancy of up to 6 months was considered normal.

We determined whether the risk factors described were significantly associated with delayed BA, delayed DA, abnormal BA, abnormal DA, and discrepancy between BA and DA by using exact chi-squared test and exact Wilcoxon–Mann–Whitney test if the total dosage received for radiation therapy was used. For analyses, we considered normal and advanced status of BA compared to CA as not delayed, severely delayed and delayed status of DA compared to CA as delayed, and normal and advanced status of DA compared to CA as not delayed.

We repeated the analyses with the smaller cohort ($n = 45$) for whom detailed exposures to craniospinal radiation therapy in Gy and steroid dose in mg/m^2 were available. It is noted that the DA of one patient in the first age group was non-diagnostic, and, hence, the patient was excluded from any analyses related to DA.

All analyses were performed with SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA). Small sample analyses were performed with StatXact-5 software (Cytel Software Corporation, copyright 2001; Cambridge, MA, USA) implemented using SAS version 9.1.

Results

Of 73 patients [34 girls (46.6%); 39 boys (53.4%)] in this study, 55 (75.3%) were Caucasians, 10 (13.7%) were African Americans, and 8 (11.0%) were of other race. The median age at the time of diagnosis for the entire cohort was 4.5 years (range: 0.1–11 years), and for the time of BA and panoramic radiograph, the median age was 9.3 years (range: 3.5–12.0 years). The median time from diagnosis of ALL to the time of study was 4.1 years (range: 0.3–11.4 years). Summaries of the distribution of BA, DA, and CA for each of the three subgroups of the total cohort and for the subcohort for whom radiation doses were available are presented in Tables 1 and 2, respectively. Among 50 patients in the first age group (< 6 years), 7 had delayed BA (14%; 95% CI, 5.8–26.7%). Among 18 patients in the second age group (between 6 and 9 years), 2 had delayed BA (11.1%; 95% CI, 1.4–34.7%). Among 5 patients in the third age group (> 9 years), 1 had delayed BA (20%; 95% CI, 0.5–71.6%). BA was normal in the vast majority of patients (61; 83.6%). We found delayed BA in 10 patients (13.7%) and advanced BA in 2 patients (2.7%). Among 50 patients in the first age group, 9 had abnormal BA (18%; 95% CI, 8.58–31.4%). Among 18 patients in the second age group, 2 had abnormal BA (11.1%; 95% CI, 1.4–34.7%). Among 5 patients in the third age group, 1 had abnormal BA (20%; 95% CI, 0.5–71.6%).

Seven of the 49 patients in the first age group (< 6 years old at the time of diagnosis) had delayed DA (14.3%; 95% CI, 6–27.2%); 1 of the 18 patients in the second age group

Table 1. Distribution of dental and skeletal developmental ages per age group at diagnosis of acute lymphoblastic leukaemia (ALL) (analysis I) in 73 paediatric patients.

	Age at diagnosis of ALL (years)		
At time of diagnosis	**Group 1 (< 6 years)**	**Group 2 (6–9 years)**	**Group 3 (> 9 years)**
Number (%) in category	50 (68.5)	18 (24.7)	5 (6.9)
Median bone age in years (range) at time of study	8.0 (3.0–13.5)	10.0 (5.0–13.0)	11.0 (10.0–12.0)
Median chronological age in years (range) at time of study	8.4 (3.4–11.8)	9.7 (6.6–11.8)	11.3 (11.1–12.0)
Median dental age in years (range) at time of study	8.8 (5.0–16.0)	9.8 (7.8–16.0)	12.0 (10.0–15.8)

Table 2. Distribution of dental and skeletal developmental ages per age group at diagnosis of acute lymphoblastic leukaemia (ALL) (analysis II) in 45 paediatric patients for whom total radiation and steroid doses were available.

	Age at diagnosis of ALL (years)		
At time of diagnosis	**Group 1 (< 6 years)**	**Group 2 (6–9 years)**	**Group 3 (> 9 years)**
Number (%) in category	35 (77.8)	8 (17.8)	2 (4.4)
Median bone age in years (range) at time of study	9.0 (4.0–13.5)	11.0 (10.0–13.0)	10.5 (10.0–11.0)
Median chronological age in years (range) at time of study	9.5 (4.9–11.8)	10.8 (9.0–11.8)	11.3 (11.2–11.3)
Median dental age in years (range) at time of study	9.0 (7.0–13.7)	11.2 (8.0–16.0)	12.9 (10.0–15.8)

(6–9 years old at diagnosis) had delayed DA (5.6%; 95% CI, 0.1–27.3%); and none of the 5 patients in the third age group (> 9 years old at diagnosis) had delayed DA (0%; 95% CI, 0–52.2%). DA was normal in just over half of the patients (41/72 = 56.9%); 8 of the 72 patients (11.1%; 95% CI, 4.9–20.7%) had a delayed DA; and 23 (31.9%) had advanced DA. The prevalence of advanced DA was more frequent than delayed DA ($P = 0.007$). Twenty-two of the 49 patients in the first age group had abnormal DA (44.9%; 95% CI, 30.7–59.8%); 7 of the 18 patients in the second age group had abnormal DA (38.9%; 95% CI, 17.3–64.3%); and 2 of the 5 patients in the third age group had delayed DA (40%; 95% CI, 5.3–85.3%).

For correlation between BA and DA, we found that 40 of the 49 patients in the first age group had abnormal discrepancy (81.6%; 95% CI, 68–91.2%); 15 of the 18 patients in the second age group had abnormal discrepancy (83.3%; 95% CI, 58.6–96.4%); 3 of the 5 patients in the third age group had abnormal discrepancy (60%; 95% CI, 14.7–94.7%). Fifty-eight of the 72 patients had age discrepancy (80.6%; 95% CI, 69.5–88.9%) of greater than 6 months; no risk factors were significantly associated with delayed BA, delayed DA, abnormal BA, abnormal DA, or discrepancy between BA and DA ($P = 0.057$).

The median radiation dose for those for whom this information was available was 18 Gy (range: 0–46 Gy). Summary statistics for the 45 patients [girls: 22 (48.9%); boys: 23 (51.1%)] for whom total radiation and steroid doses were available are presented in Table 2. We again found no statistically significant factor or a significant effect of radiation or steroid dose associated with delayed BA, delayed DA, altered BA, altered DA, or discrepancy between BA and DA ($P = 0.17$).

Discussion

There is a paucity of information addressing whether antineoplastic therapy (e.g. chemotherapy and/or radiation) alters the development of primary and permanent dentition in comparison with CA or BA. Thus, the intent of this study was to compare DA, BA, and CA, and to determine whether age at diagnosis, gender, race, treatment with or without radiation, and steroid dose impacted DA in patients treated for ALL.

CA, the standard by which maturity is often gauged, may not adequately reflect a person's biological maturity, particularly when a disease affects the developmental periods of infancy or childhood. Skeletal or biological age reflects the level of maturity achieved by the individual[24]. Average skeletal age, then, illustrates the maturation status of normal children compared with their corresponding CA[25]. Hand–wrist radiographs, used in the assessment of biological age[26], serve as a measure to determine the effects of antineoplastic therapy on skeletal development[27].

We found no statistically significant alteration of BA or DA in this modest cohort of children having been treated for ALL. We found this to be surprising because of the well-reported adverse impact of oncotherapy in childhood ALL survivors where a significant proportion of patients develop endocrinopathies that are known to alter longitudinal growth, development, and maturation[1–9].

Among the subcohort of our study for whom total radiation and steroid doses were available, we found that patients who received ≥ 8000 mg/m^2 of steroids were more likely (but not statistically significantly) to exhibit advanced dental development – compared to those patients who received < 8000 mg/m^2. The majority of the patients in this higher steroid dose group, however, exhibited normal DA. Results for the lower steroid dose group (< 8000 mg/m^2; $n = 12$) demonstrated that one (8.3%) patient had delayed dental development, and nine (75%) patients had normal dental development. Thus, while these results suggest an adverse effect of steroid dose on dental development, a definitive conclusion cannot be drawn from such a small sample size.

Treatment for ALL includes chemotherapy with contemporary therapy reserving craniospinal radiation for patients with leukaemia involving the CNS[15,16]. Among the reported effects specifically associated with ALL treatment have been an increased frequency of hypodontia, microdontia, over-retention of primary teeth, rampant decay, root stunting, and taurodontism[10]. Several studies reported numerous dental abnormalities associated with cranial irradiation. Teeth may fail to erupt as a result of radiation damage to the tooth bud before or during its development. This insult may lead to anodontia, hypodontia, disturbed eruption, deficient mineralization, and/or caries. Injury to the tooth bud from cranial irradiation has also been noted to cause occlusal disharmony and promotes growth retardation[10,11,25,27]. Clinical examination and radiographs have shown delayed development of the teeth, root dwarfism, complete failure of root development and premature apical closure, caries, general growth disturbance, enamel hypoplasia, and microdontia[10,11,28,29]. We found no correlation with craniospinal radiation exposure, nor with its dose in this study.

The severity of altered dental development has been shown to be related to the type of therapy – chemotherapy versus radiation therapy. Sex has also been identified as a significant prognostic factor in childhood ALL. The results of our study, however, indicate that patient sex is not a factor predisposing to altered BA or DA from radiation therapy.

Sonis *et al*. found that patients treated with chemotherapy but without irradiation of the CNS had the least severe disturbances to dental development compared with those who also received radiation therapy. These investigators also found that those who received 2400 cGy of radiation therapy were more severely affected, and those in the lower radiation therapy group (1800 cGy)[27]. In contrast to this study, we found no association between the total dose of radiation therapy and altered DA.

Several studies have indicated that the degree and severity of dental and craniofacial defects often depend on the child's age at diagnosis, type of CNS treatment, and the dose of cranial radiation therapy. Children who received treatment before 5 years of age sustained the most severe dental defects, indicative of an increased risk of immature teeth for developmental disturbances[27]. In contrast to a study that identified younger children as being more susceptible than their older counterparts to the trauma from radiation therapy[29], we found no significant association between age and craniospinal radiation therapy in our study.

Although novel, our study has several limitations. The study cohort was of modest size particularly when considering detailed treatment

information related to craniospinal radiation therapy and steroid doses. The modest sample size limits statistical power of the results. The retrospective nature of this study made capture of specific treatment data difficult, also contributing to a limited study population. Our findings may actually underestimate the impact of ALL therapy on DA because of the median time from diagnosis to study being about 4 years. Despite these limitations, we provide new information regarding DA in children treated for ALL; a cohort at risk for dental abnormalities and long-term therapy- and disease-associated dental sequela.

Conclusion

Previous reports have indicated that chemotherapy and radiation may contribute to delay in a patient's overall growth and development[20] as well as dental development. Although the power of our observations is limited because of the relatively small size of the cohort and retrospective study design, our findings suggest that the estimate of the proportion of abnormal DA is 43.1% [(= 31/72) with 95% CI, 31.4–55.3%] of treated children. Further large prospective study is warranted to define our observations and ultimately to determine their impact on dental and orthodontic management.

What this paper adds

- This paper presents new information regarding DA compared to BA and CA in a specialized cohort of children treated with contemporary therapy for ALL.
- This work draws attention to this complex paediatric population at risk for altered dental development as well as somatic toxicities from treatment for childhood ALL.
- It introduces the need for prospective study of this complex patient group in order to determine modifications in dental and orthodontic care that may benefit these children and adolescents.

Why this paper is important to paediatric dentists

- This paper presents important information about the correlation of BA, DA, and CA in the rapidly growing patient population of survivors of childhood ALL whose dental care will largely be provided by paediatric dentists.
- This paper presents information previously unavailable that will contribute to the dental care of this large group of paediatric patients.

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