American Journal of Hematology 80:113–118 (2005)

Bone Mineral Density and Serum Bone Turnover Markers in Survivors of Childhood Acute Lymphoblastic Leukemia: Comparison of Megadose Methylprednisolone and Conventional-Dose Prednisolone Treatments

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During recent decades, the survival rate after childhood acute lymphoblastic leukemia (ALL) has improved substantially; consequently, the long-term side effects of ALL and its treatment have gained attention, of which osteoporosis is one of the most important. The purpose of the present study was to compare the influence of different treatment protocols that include high-dose methylprednisolone (HDMP) versus conventional-dose prednisolone (CDP) for remission-induction therapy on bone mineral density (BMD) and serum bone turnover markers in survivors of childhood ALL after cessation of chemotherapy. Thirty-six boy and 23 girl survivors, treated for ALL, were cross-sectionally studied, at a mean age of 11.7 years (range 6–19). Group 1 (n = 30) received CDP therapy (prednisolone, 2 mg/kg/day, orally) and group 2 (n = 29) received HDMP therapy (prednol-L, 900–600 mg/m^2, orally). All other therapies were similar in both groups. Cranial irradiation was added for high-risk patients as soon as possible after consolidation therapy. We found that mean lumbar spine BMD z score value was –1.75 (0.83) SDS in group 1 and –1.66 (1.21) SDS in group 2. There is no difference between both groups (P = 0.736). The mean BMD z scores of prepubertal and pubertal patients were not significantly different in both groups. Comparison of serum bone turnover parameters of the patients revealed no difference between the two groups. Stepwise regression analysis revealed that lumbar spine BMD z scores was predicted by height SDS and the time past since cessation of therapy, but not age at diagnosis, BMI SDS, cranial radiotherapy, and puberty. Our study results showed that HDMP treatment did not deteriorate the bone mass any more than CDP treatment. These results proved that high-dose steroid therapy over a short period of time in remission-induction treatment would not affect the bone mass any more adversely than would conventional doses approximately 3 years after cessation of chemotherapy. Am. J. Hematol. 80:113–118, 2005.

Key words: acute lymphoblastic leukemia; ALL; children; high-dose methylprednisolone; bone mineral density; BMD; bone turnover markers

INTRODUCTION

The chance of cure in childhood cancer has improved dramatically due to intensive chemotherapy (CT) and supportive treatment during the past 30 years. The prolonged survival of children with acute lymphoblastic leukemia (ALL) has changed the focus to the various late effects of the disease and its treatment. Possible serious late effects of ALL and its treatment are second cancers, cardiac dysfunction, renal damage, pulmonary toxicity, hearing loss, dental changes, obesity, hypogonadism, growth retardation, and decreased bone mass [1–10].

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Received for publication 10 December 2004; Accepted 10 March 2005

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20438

Osteopenia can occur at diagnosis, during induction, and during maintenance therapy in patients with ALL [11–15]. It can persist for many years after completion of therapy [16]. Survivors of childhood ALL have decreased bone mineral density (BMD) even years after therapy, but it is not known for certain when osteopenia develops, whether it worsens or improves after completion of treatment, or what the long-term prognosis of bone mineralization may be. The causes of these skeletal changes are most probably multifactorial. Decreased bone mineral density may be caused by a number of factors, including the disease itself, concurrent serious infections, poor nutrition, decreased physical activity, and abnormalities in vitamin D metabolism in addition to various components of treatment—especially glucocorticoids—other chemotherapeutic agents, and radiotherapy.

Recently, the Hacettepe University Childhood Leukemia Study Group showed the significant efficacy of high-dose methylprednisolone (HDMP) in comparison with conventional-dose prednisolone (CDP) applied during remission-induction chemotherapy of ALL patients on event-free survival and relapse rate [17,18]. The purpose of the present study was to compare the influence of different steroid doses on BMD and serum bone turnover markers in survivors of childhood ALL after cessation of chemotherapy.

PATIENTS AND METHODS

Patients

In this cross-sectional study, we evaluated 108 children (68 boys and 40 girls) who were diagnosed with ALL at Hacettepe University Hospital between January 1995 and December 2000 and treated according to the current ALL protocols of Hacettepe University Childhood Leukemia Study Group, which was the St. Jude ALL Total Therapy Study XI protocol with minor modification [17,18]. The patients were divided into two groups. In order to have matched groups with respect to the time intervals after cessation of chemotherapy, 59 patients [36 boys and 23 girls; median age 11.7 years (range 6–19)] out of 108 were enrolled in the study. The only difference of the two protocols was the dose of corticosteroid during remission-induction chemotherapy: group 1 ($n = 30$) received "conventional-dose prednisolone therapy (CDP; prednisolone, 2 mg/kg/day, orally)" and group 2 ($n = 29$) received "high-dose methylprednisone therapy (HDMP; Prednol-L, 900–600 mg/m^2, orally)" (Table I). The rest of the treatment protocol was similar in both groups. Cranial irradiation (1800 cGy) was added for high-risk patients as soon as possible after consolidation therapy.

Clinical data of patients, including age at present study, age at diagnosis, sex, pubertal status, duration of chemotherapy, and duration after cessation of therapy, were recorded. In addition to these clinical parameters, the patients were also evaluated as to whether they received cranial radiotherapy (Cr RT) or not. Height and weight of the patients were measured. Body mass index (BMI = weight/stature squared, in kg/m^2) and standard deviation scores (SDS) for height (H) and BMI were calculated using the formula: (measurement [height or BMI] − mean [height or BMI] for respective sex and age)/standard deviation [height or BMI] for respective sex and age. Clinical data of the study population are shown in Table II.

TABLE I. Early Treatment Protocols of Patients*

Drug	Dose (route)	Given on days
Prednisolone (group I)	60 mg/m^2 (p.o.)	1–29
Menylprednisolone (group 2)	900 mg/m^2 (p.o.)	1–7
	600 mg/m^2 (p.o.)	8–15, 17, 19, 21, 23, 25, 29
Vincristine	1.5 mg/m^2 (i.v.)	1, 8, 15, 22
Daunorubicin	30 mg/m^2 (i.v.)	2, 8, (15)[a]
L-Asparaginase	200 U/kg (i.v., i.m.)	3, 4, 6, 8, 10, 12, (15, 17, 19)[a]
Cytosine arabinoside	300 mg/m^2 (i.v.)	22, 25, 29
Cyclophosphamide	300 mg/m^2 (i.v.)	36, 43
Etoposide	3–6 mg/kg, (i.v.)	36, 43
Methotrexate (intrathecal)	12[b], 10[c], 8[d] mg	2, 22, 43
Prednisone (intrathecal)	24[b], 20[c], 16[d] mg	2, 22, 43
Cytosine arabinoside (intrathecal)	36[b], 30[c], 24[d] mg	2, 22, 43
High-dose methotrexate[e]	50 mg/kg (i.v.)	50, 57

*Abbreviations: p.o., oral; i.v., intravenous; i.m., intramuscular.
[a]The doses in parentheses are given if bone marrow is not in remission on day 15.
[b]Given if the patient is > 3 years old.
[c]Given if the patient is 1–3 years old.
[d]Given if the patient is < 1 years old.
[e]Followed by leucoverin rescue, as with Total Study XI.

TABLE II. Clinical Data of the Study Population*

	All patients ($n = 59$)	Group 1 (CDP) ($n = 30$)	Group 2 (HDMP) ($n = 29$)	P^b
Age at diagnosis (years)[a]	5.51 (3.48)	5.69 (2.97)	5.33 (3.98)	0.696
Age at the present study (years)[a]	11.71 (3.53)	11.53 (3.62)	11.90 (3.50)	0.694
Sex, boys/girls (*n*)	36/23	15/15	21/8	—
Prepubertal/pubertal (*n*)	28/31	14/16	14/15	—
Height SDS[a]	−0.61 (0.94)	−0.78 (0.86)	−0.45 (1.00)	0.189
BMI SDS[a]	1.15 (1.41)	1.44 (1.49)	0.85 (1.28)	0.110
Duration after cessation of CT (years)[a]	3.40 (1.77)	3.16 (1.52)	3.66 (2.00)	0.294
Cr RT (*n*)	45/59	19/30	26/29	—

*Abbreviations: BMI, body mass index; BMI SDS, BMI standard deviation score; CT, chemotherapy; Cr RT, cranial radiotherapy; CDP, conventional-dose prednisolone treatment; HDMP, high-dose methylprednisolone treatment.
[a]Mean (standard deviation, SD).
[b]Comparison between groups 1 and 2.

Bone Mineral Density, Bone Biochemical, and Hormonal Status

Bone mineral densities (BMD, g/cm^2) of the lumbar spine (L_1–L_4) were measured by dual-energy X-ray absorptiometry (DEXA, QDR-4500A, Hologic, Waltham, MA) approximately 3.4 years after cessation of chemotherapy. The *z* scores, which express deviation from the mean BMD for age and sex, were also evaluated. The *z* scores for BMD were determined by comparing measurements with normal data from the manufacturer.

Blood samples were drawn in the morning for assessment of calcium, phosphate, alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D (25OHD), osteocalcin (OSC), bone-specific alkaline phosphatase (BALP), and the carboxyterminal propeptide of type I collagen (PICP). Serum calcium, phosphate, and ALP levels were measured by automatic analyzer. Serum OSC levels were measured by competitive immunoassay (Novocalcin, Metra Biosystems Inc., Mountain View, CA), serum BALP levels by immunoassay (Alkphase-B, Metra Biosystems Inc.), serum PICP levels by sandwich enzyme immunoassay (Prolagen-C, Metra Biosystems Inc.), serum PTH levels by a solid phase two-site chemiluminescent enzyme immunometric assay (Immunolyte 2000, Diagnostic Products Corp., Los Angeles, CA). Serum levels of 25OHD were measured by HPLC using kits from Chromsystems (Munich, Germany).

Statistical Analysis

Statistical analyses were carried out with the SPSS for Windows (10.0) statistical program (SPSS, Inc., Chicago, IL). Normally distributed data were expressed as means and standard deviations (SD) and were compared by Student's *t*-test. Variables not normally distributed (OSC) were expressed as medians (95% CI) and were compared by Mann–Whitney *U*-test. Linear regression analysis was performed to test associations between various variables.

RESULTS

The clinical characteristics of patients in both groups are summarized in Table II. The mean age of the patients at the time of diagnosis of ALL and at the present study was not different in both groups ($P = 0.696$ and $P = 0.694$, respectively).

In group 1, 14/30 patients were prepubertal and 16/30 were pubertal. In group 2, 14/29 patients were prepubertal and 15/29 were pubertal. No patient received replacement therapy for gonadal insufficiency in either group. Nineteen of 30 patients from group 1 and 26 of 29 from group 2 had received cranial irradiation as part of their treatment.

All patients with ALL completed their chemotherapy protocols at a mean duration of 2.7 (0.38) years. The time between cessation of therapy and present study [mean (SD)] was not significantly different in both groups [3.16 (1.52) vs. 3.66 (2.00) years; $P = 0.294$].

The mean height SDS of patients was −0.78 (0.86) in group 1 and −0.45 (1.00) in group 2 ($P = 0.189$). The mean BMI SDS of the patients in group 1 and group 2 were 1.44 (1.49) and 0.85 (1.28), respectively ($P = 0.110$) (Table II). In group 1, BMI SDS of patients who had received Cr RT was not significantly different than those who had not received Cr RT ($P = 0.541$). Also, the BMI SDS of patients who had received Cr RT in group 1 was not different than those in group 2 ($P = 0.053$) (Table III). The number of patients who had not received Cr RT in group 2 ($n = 3$) was too small to analyze statistically.

TABLE III. Serum Bone Turnover Markers of the Study Population*

	Group 1 ($n = 30$)	Group 2 ($n = 29$)	P^c
OSC (ng/mL)[a] (min-max)	12.27 (0.5–100)	15.25 (1.7–80.8)	0.683
PICP (ng/mL)[b]	279.60 (157.10)	291.58 (178.02)	0.796
ALP (U/L)[b]	504.26 (236.40)	542.32 (222.35)	0.560
BALP (U/L)[b]	100.32 (42.97)	101.29 (39.54)	0.933
PTH (pg/mL)[b]	48.28 (22.60)	46.09 (30.19)	0.779
25OHD (ng/mL)[b]	26.41 (15.73)	29.36 (12.94)	0.410

*Abbreviations: ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; CT, chemotherapy; Cr RT, cranial radiotherapy; OSC, osteocalcin; PICP, C-terminal propeptide of type I collagen; PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D.
[a]Median.
[b]Mean (SD).
[c]Comparison between groups 1 and 2.

We found that the mean lumbar spine BMD *z* score of all participants was 1.73 (0.84) below the mean. This value was −1.75 (0.83) SDS in group 1 and −1.66 (1.21) SDS in group 2. There is no difference between both groups ($P = 0.736$). The mean lumbar spine BMD *z* scores of prepubertal and pubertal patients were not significantly different in both groups ($P = 0.796$ and $P = 0.716$).

Comparison of serum bone turnover parameters of the patients revealed no difference between the two groups. Mean lumbar spine BMD *z* scores and serum bone turnover markers of the patients who had received Cr RT were not significantly different in both groups. Also, BMD *z* scores and serum bone turnover markers of the patients who had not received cranial radiotherapy of group 1 were not significantly different than those patients who had received Cr RT of group 2 (Table IV).

Factors affecting lumbar BMD *z* scores analyzed by multiple regression included height standard deviation score (HSDS), BMI SDS, duration after cessation of therapy, age at diagnosis, cranial radiotherapy, and pubertal status. Stepwise regression analysis revealed that lumbar spine BMD *z* scores were predicted by HSDS ($t = 4.58$, $P = 0.0001$) and the time passed in years since the cessation of therapy ($t = 2.80$, $P = 0{,}006$), but not with age at diagnosis, BMI SDS, cranial radiotherapy, and puberty ($t = 0.461$, $P = 0{,}646$; $t = 0.457$, $P = 0.648$; $t = -0.613$, $P = 0.542$; $t = 0.129$, $P = 0.898$, respectively)

DISCUSSION

We measured BMD at lumbar spine in 59 survivors of childhood ALL who were investigated 3.4 (1.7) years after cessation of therapy. These children belong to two groups with different steroid doses. The mean BMD *z* score of all participants was 1.73 (0.84) below the mean. We also compared the influence of HDMP versus CDP therapy on BMD in these patients. Our study showed that HDMP treatment did not have a worse effect on bone health when compared to CDP treatment in patients with ALL.

Bone mass, a result of bone formation and bone resorption, gradually increases during childhood and

TABLE IV. Clinical Characteristics and Biochemical Parameters of the Patients Who Had Received Cranial Radiotherapy in Both Groups and the Patients in Group 1 Who Had Not Received Cranial Radiotherapy*

	Group 1		Group 2		
	Cr RT(−) ($n = 11$)	Cr RT(+) ($n = 19$)	Cr RT(+) (n:26)	P_1	P_2
Age at the present study (years)[a]	11.75 (3.78)	11.97 (3.29)	12.12 (3.63)	0.382	0.898
Height SDS[a]	−0.64 (0.58)	−0.86 (0.99)	−0.42 (1.02)	0.541	0.165
BMI SDS[a]	1.01 (1.33)	1.69 (1.56)	0.82 (1.34)	0.238	0.053
BMD (g/cm^2)	0.628 (0.208)	0.578 (0.133)	0.630 (0.159)	0.895	0.826
z scores	−1.58 (0.79)	−1.85 (0.86)	−1.67 (1.27)	0.404	0.609
OSC* (ng/mL)[b]	29.76	23.17	19.26	0.374	0.511
PICP (ng/mL)[a]	306.12 (198.14)	268.4 (141.20)	291.1 (188.0)	0.579	0.667
ALP (U/L)[a]	458.00 (246.1)	522.25 (237.2)	543.8 (235.6)	0.553	0.776
BALP (U/L)[a]	90.83 (48.75)	104.32 (41.0)	99.9 (40.6)	0.467	0.736
PTH(pg/mL)[a]	40.94 (14.21)	50.32 (24.36)	48.2 (30.4)	0.424	0.818
25OHD (ng/mL)[a]	24.05 (14.27)	20.31 (10.17)	28.2 (12.1)	0.500	0.410

*Abbreviations: ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase; BMI, body mass index; BMI SDS, BMI standard deviation score; Cr RT, cranial radiotherapy; OSC, osteocalcin; PICP, C-terminal propeptide of type I collagen; PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D; P_1, comparison between group 1–Cr RT(−) and group 1–Cr RT(+); P_2, comparison between group 1–Cr RT(+) and group 2–Cr RT(+).
[a]Mean (SD).
[b]Median.

adolescence. During childhood and adolescence, bone formation prevails, while after age 40, bone resorption predominates. Chronic disease in childhood may have a negative impact on bone mineralization. The children with ALL have a period of serious illness and undergo a 2- to 3-year period of intensive treatment. To date, the negative effects of ALL and its treatment on bone mass and fracture risk are well established [19–26]. Osteopenia can occur due to therapy in patients with ALL [11–15]. Osteopenia can persist for many years after completion of therapy; however, most studies lack longitudinal data.

Halton et al. [12] measured lumbar vertebral BMD at diagnosis and every 6 months thereafter in 40 children with ALL. They found that BMD diminished linearly during the first 2 years of chemotherapy in patients older than age 11 at the time of diagnosis but remained stable in those who are younger.

Kaste et al. [16] measured lumbar spine BMD in 141 survivors of childhood ALL who were investigated 8.9–14.6 years after diagnosis and found that the BMD *z* score of participants was 0.78 standard deviations below the mean. The patients who received 18 Gy of cranial irradiation had BMD values similar to those of patients who did not receive cranial radiotherapy.

Hoorweg-Nijman et al. [26] assessed BMD in different areas (lumbar spine, femoral neck, femoral trochanter, and at 1/3 distal and ultradistal in radius) in 14 male and 10 female survivors, at a mean age of 25.1 years, treated for ALL in childhood. BMD values in the lumbar spine, femoral neck, and 1/3 distal and ultradistal in the radius were significantly lower compared to the reference population. No correlation was found between the BMD values and the cumulative dose of administered cytotoxic drugs, the age at diagnosis of ALL, or the duration of follow-up.

Nysom et al. [23,24] performed lumbar spine BMD measurements on 95 survivors of childhood ALL 11 years after diagnosis. They found that, adjusted for sex and age, the mean whole-body bone mineral content (BMC) and bone mineral areal density were significantly reduced. In these young adults, the mean height for age, bone area for height, and BMC for bone area were all reduced. They suggested that the reduced whole-body bone mass could have been caused by both reduced bone size and reduced size-adjusted bone mass. Reduced size-adjusted bone mass was not significantly related to age at diagnosis or at follow-up, length of follow-up, cranial irradiation, cumulative dose of methotrexate or corticosteroids, or endocrine status at follow-up.

In the present study, we demonstrated that young survivors of childhood ALL had reduced bone mineral density, and years after the illness, bone turnover is normal. In contrast to our study, as well as most of the data in the literature, some short-term studies showed improvement or even normalization of bone mass after treatment [28,29]. Our study also showed that lumbar spine BMD *z* scores were predicted by HSDS and the time passed since cessation of therapy, but not age at diagnosis, BMI SDS, cranial radiotherapy, or puberty. Bone mass acquisition in childhood is shown to be associated with height, weight, hormonal status, and lifestyle factors such as physical activity and calcium intake. Some of these determinants might be under genetic control as well. In healthy children and adolescents, an age-dependent increase of bone mineral density has been shown. An increase in bone density per Tanner stage was also shown in previous studies. It is possible that bone mass recovers after cessation of therapy. Besides, an increase in BMD along with height in patients with ALL is a similar finding to that of healthy children. The previous data also show that bone loss during illness and therapy tends to improve and that the relation between height and bone mass is maintained after therapy.

Glucocorticoids (GCs) are effective and necessary for childhood ALL treatment; however, they are suspected to be one of the main contributing factors of decreased bone mass. Bone loss is dependent on the type and dose of GC and occurs most prominently in the first 6 months of treatment [19,25,30]. GCs have a suppressive effect on osteoblastogenesis in the bone marrow and promote the apoptosis of osteoblasts and osteocytes, thus leading to decreased bone formation [31]. There is some evidence to suggest that GCs increase bone resorption by extending the lifespan of pre-existing osteoclasts [32]. GCs may also promote calcium loss through the kidneys and gut, and this negative calcium balance itself can lead to increased bone remodeling and osteoclastic activity due to secondary hyperparathyroidism. GCs affect both trabecular and cortical bones [33].

To our knowledge, there is no detailed study about dose-dependent effects of GCs on bone mass in patients treated for ALL. The two groups in our study had the same treatment protocol except for initial GC dose in the first month of therapy. The higher steroid dose in the HDMP group did not deteriorate the bone mass any more than in the CDP group. This shows us that high-dose steroid therapy over a short period of time during remission-induction treatment would not affect the bone mass any more adversely than the conventional doses approximately 3 years after cessation of chemotherapy. Further studies would elucidate the effects of GC dose on bone mass in the long term.

REFERENCES

1. Howard SC, Pui C. Endocrine complications in pediatric patients with acute lymphoblastic leukemia. Blood Rev 2002;16:225–243.
2. Schimiegelow M, Hertz H, Schimiegelow K, Holm K, Muller J. Insulin-like growth factor-I and insulin-like growth factor binding protein-3 during maintenance chemotherapy of acute lymphoblastic leukemia in children. J Pediatr Hematol Oncol 1999;21(4): 268–273.
3. Katz JA, Pollock BH, Jacaruso D, Morad A. Final attained height in patients successfully treated for childhood acute lymphoblastic leukemia. J Pediatr 1993;123(4):546–522.
4. Hokken-Koelaga AC, Van Doorn JW, Hahlen K, Stijnen T, Muinck Keizer-Schrama SM, Drop SL. Long-term effects of treatment for acute lymphoblastic leukemia with and without cranial irradiation on growth and puberty: a comparative study. Pediatr Res 1993;33(6):577–582.
5. Groot-Loonen JJ, Otten BJ, Hof MA, Lippens RJ, Steolinga GB. Chemotherapy plays a major role in the inhibition of catch-up growth during maintenance therapy for childhood acute lymphoblastic leukemia. Pediatrics 1995;96(4 Pt 1):693–695.
6. Schriock EA, Schell MJ, Charter M, Hustu O, Ochs JJ. Abnormal growth patterns and adult short stature in 115 long-term survivors of childhood leukemia. J Clin Oncol 1991;9(3):400–405.
7. Logghe KA, Bourguignon JP, Craen M, Benoit Y. Factors contributing to the impairment of growth in children with acute lymphoblastic leukemia. Horm Res 1988;30(2–3):62–67.
8. Moell C, Garwicz S, Marky I, Mellander L, Karlberg J. Growth in children treated for acute lymphoblastic leukemia with and without prophylactic cranial irradiation. Acta Paediatr Scand 1988; 77(5):688–692.
9. Sklar C, Mertens A, Walter A, et al. Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigray of cranial irradiation. J Pediatr 1993;123(1):59–64.
10. Schrappe M, Reiter A, Zimmermann M, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Leukemia 2000;14(12): 2205–2222.
11. Halton JM, Atkinson SA, Fraher L, et al. Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukemia. J Pediatr 1995;126(4):557–564.
12. Halton JM, Atkinson SA, Fraher L, et al. Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. J Bone Miner Res 1996;11(11): 1774–1783.
13. Van der Sluis S, Heuvel-Eibrink MM, Hahlen K, Krenning EP, de Muinck Keizer-Schrama SM. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. J Pediatrics 2002;141(2):204–210.
14. Boot AM, van den Heuvel-Eibrink M, Hahlen K, Krenning E, de Muinck Keizer-Schrama S. Bone mineral density in acute lymphoblastic leukemia. Eur J Cancer 1999;35:1693–1697.
15. Crofton PM, Ahmed SF, Wade JC, et al. Bone turnover and growth during and after continuing chemotherapy in children with acute lymphoblastic leukemia. Pediatr Res 2000;48(4): 490–496.
16. Kaste SC, Jones-Wallace D, Rose SR, et al. Bone mineral decrements in survivors of childhood acute lymphoblastic leukemia: frequency of occurrence and risk factors for their development. Leukemia 2001;15(5):728–734.
17. Yetgin S, Gurgey A, Tuncer MA, et al. A comparison of the effect of high-dose methylprednisolone with conventional-dose prednisolone in acute lymphoblastic leukemia patients with randomization. Leuk Res 1998;22:485–493.
18. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison with conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic leukemia for long-term follow-up. Leukemia 2003;17(2): 328–333.
19. Crofton PM, Ahmed SF, Wade JC, et al. Effects of intensive chemotherapy on bone and collagen turnover and the growth hormone axis in children with acute lymphoblastic leukemia. J Clin Endocrinol Metab 1998;83(9):3121–3129.
20. Arikoski P, Komulainen J, Riikonen P, Voutilainen R, Knip M, Kröger H. Alterations in bone turnover and impaired development of bone mineral density in newly diagnosed with cancer: a 1-year prospective study. J Clin Endocrinol Metab 1999;84(9): 3174–3181.
21. Arikoski P, Komulainen J, Voutilainen R, et al. Reduced bone mineral density in long-term survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 1998;20(3): 234–240.
22. Tillmann V, Darlington ASE, Eiser C, Bishop NJ, Davies HA. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Miner Res 2002;17(6): 1073–1080.
23. Nysom K, Holm K, Michaelsen KF, Hertz H, Muller J, Molgaard C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 1998;16:3752–3760.
24. Nysom K, Holm K, Hertz H, Muller J, Michaelsen KF, Molgaard C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. J Clin Oncol 2001;19(11):2970–2971.
25. Ahmed SF, Wallace WH, Crofton PM, et al. Short-term changes in lower leg length in children treated for acute lymphoblastic leukemia. J Pediatr Endocrinol Metab 1999;12:75–80.
26. Haddy TB, Mosher RB, Reaman GH. Osteoporosis in survivors of acute lymphoblastic leukemia. Oncologist 2001;6:278–285.
27. Hoorweg-Nijman JJG, Kardos G, Roos JC, et al. Bone mineral density and markers of bone turnover in young adult survivors of childhood lymphoblastic leukemia. Clin Endocrinol 1999;50: 237–244.
28. Boot AM, de Ridder MAJ, Pols HAP, Krenning EP, de Muink Keizer-Schrama SMPF. Bone mineral density in children and adolescence: relation to puberty, calcium intake and physical activity. J Clin Endocrinol Metab 1997;82:57–62.
29. Gilsanz V, Carlson ME, Roe TF, Ortega JA. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. J Pediatr 1990; 117:238–244.
30. Mushtag T, Ahmed SF. The impact of corticosteroids on growth and bone health. Arch Dis Child 2002;87:93–96.
31. Weinstain RS, Jilka RL, Parfitt AM, et al. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest 1998;102:274–282.
32. Hofbauer LC, Gori F, Riggs BL, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in human osteoblastic lineage cells: potential paracrine mechanisms of glucocorticoid-induced osteoporosis. Endocrinology 1999;140:4382–4389.
33. Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. J Clin Oncol 2001;19: 3066–3072.