Bone mineral density in survivors of childhood acute lymphoblastic leukemia

Fani Athanassiadou[1], Athanassios Tragiannidis[1], Israel Rousso[1], Georgios Katsos[2] Vassiliki Sidi[3], Theodotis Papageorgiou[1], Christos Papastergiou[4], Ioannis Tsituridis[4] Dimitrios Koliouskas[3]

[1]Hematology-Oncology Unit, 2nd Pediatric Department, AHEPA Hospital, and Departments of [2]1st Pediatrics, and [3]Pediatric Oncology, Hippokration Hospital, and [4]Department of Radiology, Papageorgiou Hospital, Thessaloniki, Greece

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The aim of our study was to evaluate bone metabolism with measurement of bone mineral density (BMD) after management (chemo-, radiotherapy) for childhood acute lymphoblastic leukemia (ALL).

Bone mineral density (g/cm^2) of lumbar spine was measured by dual energy X-ray absorptiometry (Norland bone densitometer) in 18 children with ALL and a median of 34 months' post-diagnosis with no history of relapse, secondary malignancy, or transplantation. In addition, patients' BMDs were correlated with particular attention to age, sex and time (years) from completion of chemotherapy. The results were compared with healthy age- and sex-matched controls of the same population and expressed as standard deviation scores (SDS).

Mean age of children was 9.8±3.7 years. Of 18 children (10 boys and 8 girls), 13 were grouped as standard and 5 as high-risk, respectively. Based on z-score values, 9 were classified as normal (z-score <1 SD), 7 as osteopenic (z-score 1-2.5 SD) and 2 as osteoporotic (z-score >2.5 SD). Children with ALL had reduced lumbar BMDs (z score –0.99) in comparison to healthy controls (z score –0.14) (p=0.011), which is indicative of relative osteopenia. Moreover, the reduced BMD was associated with patient age (z score –0.14 and –1.52 for ages <10 and >10 years, respectively, p=0.016). Reduced BMD was not correlated with time from completion of chemotherapy (p=0.33), risk group (p=0.9) and sex (p=0.3). We conclude that children's BMDs are reduced after completion of chemotherapy for ALL. The causes are multifactorial and mainly related to antineoplastic treatments, such as corticosteroids and methotrexate, physical inactivity and cranial irradiation. We suggest that further studies are needed to evaluate the long-term effect on BMD in these children and to prevent pathological fractures later in life.

Key words: osteopenia, osteoporosis, bone mineral density, acute lymphoblastic leukemia, childhood.

In the last decades there has been a significant increase in EFS (event free survival) and OS (overall survival) in children with acute lymphoblastic leukemia (ALL). As survival rates for childhood ALL have radically improved, late effects associated with the successful but highly intensive chemotherapy and/or radiotherapy have dramatically increased[1]. Osteopenia and osteoporosis are known to occur frequently in children at diagnosis, during and after completion of chemotherapy[1]. Moreover, many studies in the literature have reported pathological fractures during and after therapy, osteonecrosis and skeletal abnormalities[2].

Bone homeostasis is controlled by bone remodeling, a process characterized by two antagonistic activities: formation and resorption of bone caused by osteoblasts and osteoclasts,

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respectively. This remodeling process is initiated by the activation of osteoclasts, followed by the filling in of the resorption cavity by bone deposited by osteoblasts. The way in which these events are regulated is still only partially understood, but cytokines, growth factors and hormones are known to be involved.

Many possible responsible factors have been associated with osteopenia and osteoporosis in children with ALL[1,3]. Glucocorticoids represent the main factor, although many recent studies have proposed other chemotherapeutic agents such as methotrexate and 6-mercaptopurine[4,5]. Moreover, cranial irradiation represents another responsible factor for the development of osteopenia/osteoporosis[6,7].

Therefore, the aim of our prospective study was to measure bone mineral density (BMD) in a group of childhood ALL survivors and to compare our results with those of their healthy controls.

Material and Methods

We studied 18 children with ALL who completed their chemotherapy/radiotherapy treatment in the Hematology-Oncology Unit of the 2nd Pediatric Department of Aristotle University of Thessaloniki and who had a median of 34 months' post-diagnosis with no history of relapse, secondary malignancy, or transplantation. Informed consent was obtained from parents or legal guardians of the children.

All children were treated according to ALL BFM'95 protocol and were grouped as standard, intermediate or high risk, respectively. Standard risk chemotherapy protocol involved prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytosine arabinoside, 6-mercaptopurine, thioguanine, high dose methotrexate, doxorubicin and dexamethasone, and in the high-risk group additional vindesine, ifosfamide and etoposide. High and intermediate (only children with T-ALL) risk protocol also involved cranial irradiation as central nervous system (CNS) prophylaxis. Lumbar spine (L2-L4) BMD (g/cm^2) was measured by dual energy X-ray absorptiometry (Norland bone densitometer). All measurements were performed as recommended by the manufacturer of the unit. Results were expressed as age- and sex standardized z scores [mean (95% confidence intervals)][1,8]. Results were compared with those of 18 healthy controls and expressed as age- and sex- standardized mean z scores. Comparisons were made using an independent samples t-test by SPSS statistical package (version 7.5) and significance was established at $p<0.05$.

Results

The mean age of children was 9.8±3.7 years. Of 18 children (10 boys and 8 girls), 13 were grouped as standard and five as high-risk, respectively. Based on z-score values, nine were classified as normal (z-score <1 SD), seven as osteopenic (z-score 1-2.5 SD) and two as osteoporotic (z-score >2.5 SD).

Children with ALL had reduced lumbar BMDs (z score –0.99) in comparison to healthy controls (z score –0.14) (p=0.011), which is indicative of relative osteopenia. Moreover, the reduced BMD was associated with patient age (z score –0.14 and –1.52 for ages <10 and >10 years, respectively, p=0.016). Reduced BMD was not correlated with time from completion of chemotherapy (z score –0.89 and –0.36 for chemotherapy completion <2 and >2 years, respectively, p=0.33), risk group (z score –0.97 and –1.02 for standard/intermediate and high risk, respectively, p=0.2) and sex (z score –0.13 for boys and –1.00 for girls, p=0.3). Our results are shown in Table I.

Table I. Z scores data of the study population

	Z scores	p
ALL/controls	-0.99/-0.14*	0.011
Boys/girls	-0.13/-1.00	0.3
Time of completion of treatment (<2/>2 years)	-0.89/-0.36	0.33
Age (<10/>10 years)	-0.14/-1.52*	0.016
Risk group (standard, intermediate/high)	-0.97–1.02	0.9

*p<0.05.

Discussion

Many studies in the literature have demonstrated that children affected by ALL are osteopenic/osteoporotic at all phases: at diagnosis, during treatment and mainly after completion of treatment[1]. The pathogenesis of osteopenia/osteoporosis is multifactorial and the main risk factors include leukemic invasion of the bone, corticosteroid and methotrexate treatment, cranial irradiation, hormone deficiency, malnutrition and prolonged physical inactivity[4-7,9]. BMD measurement of the lumbar vertebrae represents the most important diagnostic tool in current use for diagnosing osteopenia/osteoporosis, which keeps the amount of radiation exposure low.

The BMD and the respective z score after completion of treatment found in our study show that children with ALL have z scores indicative of relative osteopenia; a statistical significance was determined in comparison with z scores of their healthy controls. Arikoski et al.[7,10,11] and Warner et al.[5] also reported that children with ALL are osteopenic after completion of treatment. The reduced BMD of children with ALL in our study was correlated with patient's age, and children aged >10 years presented a more pronounced osteopenia. This is probably due to the fact that the maximum increment rate of bone occurs later in life (>15 years). Another possible factor is that among this group of children (>10 years), the bone density z score was particularly pronounced (>2.5 SD) in two patients with known pituitary insufficiency due to cranial irradiation.

Our data demonstrated that lumbar BMD was decreased in girls, but no statistical significance was found in comparison with boys' values. Arikoski et al.[7,11] also found reduced BMD for girls, although the majority of studies did not determine a correlation of reduced BMD with patient's sex.

Many hypotheses have been proposed for bone metabolism abnormalities in children with ALL after completion of treatment. Although it is well known that bone metabolism is disturbed at diagnosis, recent studies demonstrated that there is a modification or inhibition of molecular mechanisms that control osteoblast and osteoclast activity as a result of chemotherapy that leads to a defective bone mineralization.

Treatment represents the most important pathogenic factor. Corticosteroids have been proposed to increase bone resorption due to an increase in urinary calcium excretion and a decrease in intestinal calcium absorption. Moreover, glucocorticoids inhibit the expression of the vitamin D receptor and of osteocalcin, which represents the principal bone matrix protein[4,7]. The vertebrae, which are mainly composed of trabecular bone (66% versus 34% for cortical bone), are more affected by corticosteroids in comparison to cortical bone presented in the femoral neck (25% for trabecular bone versus 75% for cortical bone). Many studies in the literature have shown that bone loss after long corticosteroid administration is most rapid in trabecular bone[5,10].

Another chemotherapeutic agent involved in the pathogenesis of osteopenia/osteoporosis is methotrexate, which appears to increase bone resorption and excretion[12-14]. Recent data have also implicated 6-mercaptopurine in the pathogenesis of osteopenia/osteoporosis, although the mechanism by which 6-mercaptopurine induces bone loss remains unknown[5].

History of cranial irradiation and impaired pituitary function suggest that hormone deficiency (mainly growth hormone and gonadotropins) might disturb the normal skeletal growth of children affected by ALL[15]. Gilsanz et al.[9] demonstrated a 10% reduction in bone mineralization in the lumbar spine in children affected by ALL.

Moreover, malnutrition in children with ALL, which leads to calcium malabsorption and vitamin D metabolism alteration, has been shown to impair bone formation directly and increase bone resorption. In addition, prolonged physical inactivity mainly during induction and reinduction chemotherapy has also been determined as another significant risk factor for the development of osteopenia/osteoporosis because development of skeletal mass in healthy children has been associated with activity patterns[16,17].

We conclude that BMD is reduced after completion of chemotherapy in children with ALL. The causes are multifactorial and mainly related to antineoplastic treatments, such as corticosteroids and methotrexate, physical inactivity and cranial irradiation. We suggest that further studies are needed to evaluate the long-term effect on BMD in these children and to prevent pathological fractures later in life.

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