Bone metabolism and mineralisation after cytotoxic chemotherapy including ifosfamide

J de Schepper, S Hachimi-Idrissi, O Louis, R Maurus, J Otten

Abstract
Lumbar spine bone mineral density and bone mineral metabolism were studied in 13 children three months or more after completion of cytotoxic chemotherapy that included ifosfamide for different malignancies. Blood and urine were analysed for calcium, phosphorus, and magnesium and blood for alkaline phosphatase activity, parathyroid hormone, and 1,25(OH)2 vitamin D3. Bone mineral density (BMD) was measured at the lumbar spine (L1–L4) using a commercial dual x ray absorptiometer. Serum concentrations of calcium, phosphorus, and magnesium and alkaline phosphatase activity, as well as plasma 1,25(OH)2 vitamin D3 concentrations were normal in all children. Slightly raised parathyroid hormone concentrations were seen in two children. An increased urinary excretion of calcium was found in five children. Mean (SD) BMD of the children was 0.88 (1.44). Three children had osteopenia, as defined by a BMD lower than 2 SD for age and sex related standards. No significant relation was found between the BMD and the biochemical parameters. In conclusion, a normal BMD was found in most patients who had received ifosfamide, even in those with persisting hypercalcaemia.

Ifosfamide is increasingly being used to treat solid tumours in children and has become frontline treatment of soft tissue sarcomas.1 Its side effects include transient and permanent tubular damage, leading to metabolic acidosis, renal phosphate loss, and hypercalcaemia, which in turn lead to a defective bone mineralisation in growing children. Therefore, we screened children who received chemotherapy including ifosfamide for an insufficient bone mineralisation and abnormalities in the bone mineral metabolism.

Patients and methods
Thirteen patients or their parents gave their informed consent for the study. The characteristics of the patients and the treatment received are shown in Table 1. The age of the patients ranged between 2-9 and 17-4 years at the time of the study, which was performed between three and 147 months after completion of chemotherapy.

All patients, who had received various cytotoxic treatments (but all including ifosfamide) given for different malignancies (in most cases a rhabdomyosarcoma), were off any medical treatment at the time of the study. One patient had presented a malignant hypercalcaemia at the start of the treatment (patient 7), whereas another child had been treated for ifosfamide related hypophosphataemic rickets one year previously for three months (patient 1). Two patients (patients 5 and 9) had received respectively cerebral and axillary irradiation as part of their treatment. Bone mineral density (BMD) was measured at the level of the lumbar spine (L1–L4) by dual x ray absorptiometry with a commercial densitometer (Hologic QDR 1000/W, Waltham, USA). Lumbar spine

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<th>Time lapse from last ifosfamide (months)</th>
<th>Total dose of ifosfamide (g/m²)</th>
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<td>Correspondence to: Dr J de Schepper, Division of Paediatric Endocrinology, Department of Paediatrics, University Hospital VUB, Laarbeeklaan 101, B-1090 Brussels, Belgium.</td>
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*All patients also received vincristine and actinomycin D. Doxorubicin hydrochloride given as Adriamycin. VP-16=etoposide.
BMD measurements with this equipment have a reproducibility of 0.3% in vitro and of 1% in vivo in adults. The entrance radiation dose received by the child during the examination is less than 5 mRem. Results of BMD measurements were expressed as g hydroxyapatite/cm² (gHA/cm²). SD scores of BMD for chronological age were calculated using the reference values established with the same apparatus in children by Glastre et al. Blood and urine were analysed for calcium, phosphorus, and magnesium concentrations and blood also for alkaline phosphatase activity by standard automated chemical procedures. Intact parathyroid hormone and 1,25(OH)₂ vitamin D₃ concentrations were determined by commercial radioimmunoassay procedures (Nichols Institute, San Juan Capistrano, CA, USA). The study was approved by the ethical committee of the hospital. Statistical analysis included the Student’s t test and linear regression analysis.

Results
As shown in table 2, serum concentrations of calcium, phosphorus and magnesium and alkaline phosphatase activity were normal in all children. While 1,25(OH)₂ vitamin D₃ was normal in all patients, slightly raised parathyroid hormone concentrations were seen in two children (patients 7 and 12). An increased urinary excretion of calcium was found in five children. The excretion of the other minerals was normal in all children.

As shown in the figure, lumbar spine BMD of the patients increased with age as in normal children. Mean (SD) BMD of the patients, expressed as SD score for age, was -0.88 (1.44). Three children had a lumbar spine BMD lower than 2 SD for age (table 2), and hypercalciuria was present in two of these children. For the total group, no significant correlation could be found between the BMD SD score and the biochemical parameters. The degree of osteopenia, as reflected by the BMD SD score, was not related to the age of the patient, the duration of the chemotherapy, the time lapse between completion of treatment, and the time of the study. The two patients with previous irradiation as part of their treatment had a lumbar spine BMD within normal limits.

Discussion
Although monitoring of the renal tubular function in ifosfamide treated children has been proposed to predict and possibly prevent severe bone disease, few studies exist on the bone mineralisation of ifosfamide treated children or adults. Radiological signs of rickets have been reported in five out of 44 children treated with ifosfamide for a Wilms' tumour and in two out of 11 children who had received ifosfamide for a soft tissue sarcoma. Standard skeletal radiographs cannot detect bone loss as long as the bone mineral content has not decreased by 30 to 50%.

We evaluated the bone mineralisation by dual x ray absorptiometry, which is both more sensitive and more accurate than standard radiology. The lumbar spine was chosen as the site of measurement because of its high content of trabecular bone, which is more sensitive to metabolic changes than cortical bone of the extremities. By this technique, an abnormally
low BMD was found in 3/13 patients several months after completion of chemotherapy. None of these osteopenic children had received vertebral or cranial irradiation, which may be a risk factor for bone demineralisation in leukaemia.14 One of these three osteopenic children had received prednisolone and methotrexate, both of which have been considered to cause bone demineralisation in children with leukaemia.15

Renal bicarbonate, calcium, and phosphate wastage and abnormalities in the vitamin D metabolism are held responsible for the metabolic bone disease associated with severe proximal tubular dysfunction.16 These abnormalities were mostly present in the reported children with hypophosphataemic rickets induced by ifosfamide. In our study, two of the three children with osteopenia presented with a significant hypercalcaemia, but none had an increased phosphate loss in the urine. Two arguments against hypercalcaemia playing a major part in the mechanism of deficient bone mineralisation after ifosfamide treatment are: (1) the absence of any relationship between the degree of calcification and bone mineralisation and (2) the persistence of hypercalcaemia in children who had developed clinical rickets after ifosfamide and are cured of this disease.17 18

In accordance with most previous reports, no important abnormalities of the calcium regulating hormones were found.3 Undetectable concentrations of 1,25 (OH)2 vitamin D3 have been observed in some patients treated with ifosfamide for a Wilms' tumour. In these patients, however, the interpretation of the results may be confounded by the possible role of other components of the treatment such as nephrectomy and irradiation of the remaining kidney. Further studies, including baseline measurements of BMD and bone mineral metabolism before chemotherapy as well as follow-up measurements during and after stopping chemotherapy, are needed to understand the mechanism of osteopenia in some of the ifosfamide treated children.

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