Archives of Disease in Childhood 1994; 71: 346–348

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 given 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 D_3. 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 D_3 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 hypercalciuria.

(*Arch Dis Child* 1994; 71: 346–348)

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 hypercalciuria, which in turn lead to a defective bone mineralisation in growing children.[2 10] 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

Table 1 Characteristics of patients studied and treatment received

Patient No	*Sex*	*Age (years)*	*Disease status*	*Irradiation*	*Time lapse from last ifosfamide (months)*	*Total dose of ifosfamide (g/m^2)*	*Other cytotoxic agents**
1	F	3·7	Embryosarcoma	No	18	60	–
2	M	2·9	Rhabdomyosarcoma	No	6	60	–
3	F	3·3	Rhabdomyosarcoma	No	4	60	–
4	F	6·1	Rhabdomyosarcoma	No	15	12·5	Carboplatin, epirubicin, VP-16, cyclophosphamide, doxorubicin hydrochloride
5	F	6·4	Rhabdomyosarcoma	Yes	51	12	Doxorubicin hydrochloride, cyclophosphamide, cisplatin
6	M	10·3	Rhabdomyosarcoma	No	39	60	–
7	M	8·3	B cell leukaemia	Yes	12	12·7	Doxorubicin hydrochloride, cyclophosphamide, methotrexate, prednisolone, VP-16
8	M	9·5	B cell leukaemia	No	5	12·0	Doxorubicin hydrochloride, cyclophosphamide, methotrexate, prednisolone, VP-16
9	M	9·5	Rhabdomyosarcoma	No	17	60	Carboplatin, epirubicin, VP-16
10	M	17·4	Rhabdomyosarcoma	No	29	24	Vindesine, cisplatin, doxorubicin hydrochloride, methotrexate
11	M	13·8	Synovialis sarcoma	No	147	36	–
12	M	14·4	Osteosarcoma	No	12	12	Carboplatin, epirubicin, VP-16, cyclophosphamide, doxorubicin hydrochloride
13	F	13·3	Rhabdomyosarcoma	No	3	60	–

*All patients also received vincristine and actinomycin D. Doxorubicin hydrochloride given as Adriamycin. VP-16=etoposide.

Akademisch Ziekenhuis, Vrije Universiteit Brussel, Brussels, Belgium, Department of Paediatrics
J de Schepper
S Hachimi-Idrissi
R Maurus
J Otten

Department of Radiology
O Louis

Correspondence to:
Dr J de Schepper, Division of Paediatric Endocrinology, Department of Paediatrics, University Hospital VUB, Laarbeeklaan 101, B-1090 Brussels, Belgium.

Accepted 25 May 1994

Table 2 Results of determinations showing calcium and phosphorus metabolism and BMD measurements

	Serum					*Urine*			
Patient No	*Calcium (mmol/l)*	*Phosphorus (mmol/l)*	*Alkaline phosphatase (U/l)*	*Parathyroid hormone (ng/l)*	*1,25(OH)$_2$ vitamin D$_3$*	*Calcium (mmol/mmol creatinine)*	*TmPO$_4$/GFR (mmol/LGF)**	*BMD (gHA/cm^2)*	*BMD (SD score)*
1	5·0	1·45	530	11·3	199	5·4	1·227	0·38	−2·80
2	4·9	1·58	430	5·7	204	2·6	1·227	0·41	−1·81
3	4·8	1·61	323	16·1	204	0·69	1·614	0·38	−2·41
4	4·9	1·61	430	18·1	156	0·56	1·647	0·48	−0·24
5	4·8	1·61	321	17·6	204	0·6	1·582	0·56	1·45
6	5·2	1·48	381	15·2	156	5·1	1·388	0·57	1·66
7	4·6	1·51	306	41·8	170	0·5	1·550	0·68	0
8	4·7	1·51	343	26·1	211	0·72	1·873	0·45	−2·80
9	4·7	1·51	320	10·8	213	9·8	1·292	0·58	−0·58
10	4·5	1·29	320	22·6	129	0·4	1·614	0·79	−1·31
11	4·9	1·38	270	18·0	151	0·4	1·292	0·89	−1·00
12	4·6	1·38	657	39·9	175	0·2	1·453	0·70	−1·49
13	4·7	1·28	520	34·5	185	0·3	1·345	0·76	−0·11
Normal range	3·8–5·2	1·1–2·2	250–750	10–35	50–150	0·02–0·69	1·15–2·44		

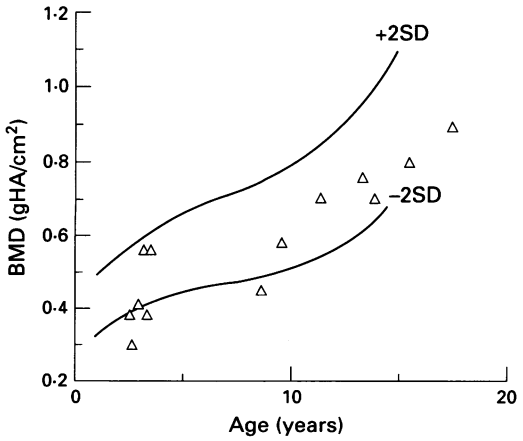
*TmPO$_4$/GFR=tubular maximum rate of phosphate reabsorption in relation to glomerular filtration rate (LGF=litre of glomerular filtrate).

BMD measurements with this equipment have a reproducibility of 0·3% in vitro and of 1% in vivo in adults.[11 12] 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/cm^2 (gHA/cm^2). SD scores of BMD for chronological age were calculated using the reference values established with the same apparatus in children by Glastre *et al.*[13] 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 D$_3$ 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 D$_3$ 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.



Lumbar spine BMD, expressed as gHA/cm^2, in relation to the age of the patients.

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.[3 4] 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 hypercalciuria, but none had an increased phosphate loss in the urine. Two arguments against hypercalciuria 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 calciuria and bone mineralisation and (2) the persistence of hypercalciuria 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 D_3 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.

We wish to thank Dr C Sevens and Dr J Smitz for providing the facilities for the laboratory examinations and Mrs A Schouppe for preparing the manuscript.

1 De Kraker J, Voute P. Ifosfamide, mesna and vincristine in pediatric oncology. A phase II study. *Cancer Treat Rev* 1983; **10:** 165–6.
2 Smeitink J, Verreussel M, Schröder C, Lippens R. Nephrotoxicity associated with ifosfamide. *Eur J Pediatr* 1988; **148:** 164–6.
3 Skinner R, Pearson ADJ, Price L, Coulthard MG, Craft AW. Nephrotoxicity after ifosfamide. *Arch Dis Child* 1990; **65:** 732–8.
4 Burk CD, Restaino I, Kaplan BS, Meadows AT. Ifosfamide-induced renal tubular dysfunction and rickets in children with Wilms' tumor. *J Pediatr* 1990; **117:** 331–5.
5 Heney D, Wheeldon J, Rushworth P, Chapman C, Lewis IJ, Bailey CC. Progressive renal toxicity due to ifosfamide. *Arch Dis Child* 1991; **66:** 966–70.
6 Rossi R, Helmchen U, Schellong G. Tubular function and histological findings in ifosfamide-induced renal Fanconi syndrome – a report of two cases. *Eur J Pediatr* 1992; **151:** 384–7.
7 De Schepper J, Hachimi-Idrissi S, Verboven M, Piepsz A, Otten J. Renal function abnormalities after ifosfamide treatment in children. *Acta Paediatr* 1993; **82:** 373–6.
8 Goulding A, Campbell DR. Dietary NaCl loads promote calciuria and bone loss in adult oophorectomized rats consuming a low calcium diet. *J Nutr* 1983; **113:** 1409–14.
9 Oliveri MB, Cassinelli H, Bergada C, Mautalen CA. Bone mineral density of the spine and radius shaft in children with X-linked hypophosphatemic rickets (XLH). *Bone Miner* 1991; **12:** 91–100.
10 Brenner RJ, Spring DB, Sebastian A, *et al.* Incidence of radiographically evident bone disease, nephrocalcinosis and nephrolithiasis in various types of renal tubular-acidosis. *N Engl J Med* 1982; **307:** 217–22.
11 Pacifici R, Rupich R, Vered I, *et al.* Dual energy radiograph (DER): a preliminary comparative study. *Calcif Tissue Int* 1988; **43:** 189–91.
12 Kelly TL, Slovik DM, Schoenfeld DA, Neer RM. Quantitative digital radiography versus dual photon absorptiometry of the lumbar spine. *J Clin Endocrinol Metab* 1988; **67:** 839–44.
13 Glastre C, Braillon P, David L, Cochat P, Meunier PJ, Delmas PD. Measurement of bone mineral content of the lumbar spine by dual energy X-ray absorptiometry in normal children: correlations with growth parameters. *J Clin Endocrinol Metab* 1990; **70:** 1330–3.
14 Gilsanz V, Carlson ME, Roe TF, Ortega JA. Osteoporosis after cranial irradiation for acute lymphoblastic leukemia. *J Pediatr* 1990; **117:** 238–44.
15 Atkinson SA, Fraher L, Gundberg CM, Andrew M, Pai M, Barr RD. Mineral homeostasis and bone mass in children treated for acute lymphoblastic leukaemia. *J Pediatr* 1989; **114:** 793–800.
16 Stanbury SW, Lumb GA. Metabolic studies of renal osteodystrophy. *Medicine (Baltimore)* 1962; **41:** 1–19.
17 Van Gool S, Brock P, Vijndaele G, *et al.* Reversible hypophosphatemic rickets following ifosfamide treatment. *Med Pediatr Oncol* 1992; **20:** 254–7.
18 De Schepper J, Stevens G, Verboven M, Baeta C, Otten J. Ifosfamide-induced Fanconi's syndrome with growth failure in a 2-year-old child. *Am J Pediatr Hematol Oncol* 1991; **13:** 39–41.