Pergamon

European Journal of Cancer, Vol. 34, No. 2, pp. 260–262, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10135-6

Original Paper

Bone Loss Induced by Cancer Treatment and its Management

P.D. Delmas and A. Fontana

INSERM Research Unit 403, Hôpital Edouard Herriot Pav F, 69437 Lyon Cedex 03, France

INTRODUCTION

BONE METABOLISM is characterised by two opposite activities, the formation of new bone by osteoblasts and the resorption of old bone by osteoclasts. Both are normally tightly coupled in time and space and bone mass depends on the balance between resorption and formation. Cancer itself may induce bone loss. Studies of biological markers of bone turnover have shown increased bone resorption in patients presenting cancer without bone metastases. Breast carcinoma and other tumours increase osteoclastic activity probably by increasing the release of transforming growth factor (TGF α or β), parathyroid hormone related protein (PTHrp) and cytokines. Cancer treatment may also have direct or indirect effects on bone loss. With the improvement in cancer treatment, the number of long term survivors increases and the long term consequences of adverse effects of treatment on bone become significant. In particular, osteoporosis is now a common finding in long term survivors from breast cancer, the diagnosis and management of which is a source of problems for the clinician.

DIRECT EFFECTS OF CANCER TREATMENT ON BONE LOSS

The direct effects of the chemotherapeutic agents doxorubicin and methotrexate have been studied in the rat [1]. Histomorphometric analysis of bone revealed a reduction of osteoid parameters with a decrease in the absolute osteoid volume but with no change in osteoblastic surfaces suggesting that the matrix produced per osteoblast was reduced. Resorption parameters were increased with methotrexate and unchanged with doxorubicin. The trabecular bone volume was markedly reduced by both treatments and the overall bone formation rate was decreased by approximately 60%. Thus, these chemotherapeutic agents appear to have adverse effects on bone remodelling, especially on bone formation.

A direct effect of suppressive thyroxine therapy on bone loss in patients with thyroid cancer has also been reported [2]. Hyperthyroidism is a classical cause of osteoporosis and thyroxine therapy is often associated with subclinical hyperthyroidism. Several studies of the effects of suppressive dose of thyroxine on bone density have been conducted, with conflicting results. A recent meta-analysis including 33 studies of the effects of thyroid hormone therapy (suppressive or replacement therapy) on bone mass has concluded that suppressive thyroid hormone therapy is associated with significant bone loss in postmenopausal women. Bone mineral density (BMD) was reduced, on average, by 7% at the lumbar spine, 5% of the femoral neck and 9% of the trochanter of the hip. The theoretical risk of hip and spine fracture was approximately 1.6 higher in postmenopausal women treated by suppressive thyroid therapy than in controls [3].

Glucocorticoids are widely used in cancer especially to control emesis induced by chemotherapy. In haematological malignant diseases, glucocorticoids are also often used in association with other chemotherapeutic agents e.g. dexamethasone in multiple myeloma. A large dose of glucocorticoids induces rapid and severe bone loss, resulting in osteoporotic fractures through two mechanisms. A dose-dependent inhibition of bone formation has been widely documented. An increase in osteoclastic bone resorption may occur with high-doses either directly or indirectly through secondary hyperparathyroidism related to the effects of glucocorticoids on calcium transport at the gut and kidney [4].

INDIRECT EFFECTS OF CANCER TREATMENT ON BONE LOSS

Cancer treatment has also indirect effects on bone loss; indeed, chemotherapy may induce hypogonadism and castration (surgical or by radiotherapy) is commonly used.

Hypogonadism in men is known to induce bone loss with a large decrease of BMD during the first 2 years, approximately 7% per year [5]. This effect has been reported in men treated for Hodgkin's disease in whom BMD was measured, on average, 3–4 years after chemotherapy [6]. Men were in complete remission and all had azoospermia with raised LH (luteinising hormone) and FSH (follicle stimulating hormone) levels but no significant decrease in testosterone level. BMD was significantly reduced at the lumbar spine, femoral neck and forearm with a positive correlation between serum testosterone level and lumbar spine and femoral neck BMD. Osteoporosis after orchidectomy for prostate cancer has also been reported [7]. Approximately 4% of men treated by orchidectomy had osteoporotic fractures with a decrease of femoral neck BMD versus 1% in men without orchidectomy. Bone loss has also been observed in women treated for Hodgkin's disease [8]; young women with premature ovarian

failure induced by treatment had the same BMD compared with older postmenopausal women, but had a significantly lower BMD compared with those with a normal ovarian function after treatment. Oestrogen deficiency induced accelerated bone loss within 5–8 years followed by a linear rate of bone loss. The age-related decrease in osteoblast activity within each remodelling unit combined with an increase in the number of remodelling units activated per unit time explain the magnitude of bone loss in postmenopausal women.

PREVENTION OF OSTEOPOROSIS IN PATIENTS WITH CANCER

Oral contraceptives have been used to protect ovarian function in premenopausal women treated for Hodgkin's disease [9]. Chemotherapy often induces ovarian failure with destruction of ova and follicular elements of ovary. When oral contraceptives were started at the time of chemotherapy, ovarian biopsies made after treatment did not show a decreased number of follicles contrasting with findings in untreated women. Amongst the various treatments of osteoporosis, bisphosphonates and oestrogen (in postmenopausal women) appear to be the most effective ones. Hormone replacement therapy (HRT) is effective in slowing bone loss. During the first 2 years, HRT induces a significant increase in BMD which is more pronounced in cancellous bone than in cortical bone. Although the effects of HRT on incident fractures has been studied in a few studies, cohort and case control studies suggest strongly that HRT decreases significantly osteoporotic fractures. In most studies, the relative risk of vertebral, hip and wrist fractures ranges from 0.3 to 0.8 with an average of 0.6 [10].

Bisphosphonates are synthetic compounds which decrease bone resorption. They are known to prevent bone loss in a number of experimental osteoporosis models. They decrease bone turnover and increase bone balance at the basic multicellular unit (BMU) level. Several clinical studies have shown an increased bone mineral density under bisphosphonate therapy and etidronate and alendronate are currently used in the treatment of osteoporosis. The use of bisphosphonates in cancer patients is discussed elsewhere in this issue (see Body, pp. 263–269).

BREAST CANCER AND BONE LOSS

Osteoporosis in breast cancer patients is a growing problem because it is the most frequent cancer in women and because relatively long survival is common. Seventy-one per cent of women after adjuvant chemotherapy for premenopausal breast cancer have premature ovarian failure and their BMD is significantly decreased compared with premenopausal women with breast cancer not treated by adjuvant chemotherapy [11]. Thus, the occurrence of vertebral and other fractures in breast cancer patients is not always due to bone metastases, but can be related to osteoporosis. In such patients, osteoporotic fracture may be difficult to differentiate from bone metastatic fracture. Bone scintigraphy could be helpful in the presence of multiple areas of increased uptake. Magnetic resonance imaging, particularly in vertebral lesions, can differentiate benign fracture from malignant ones by detecting malignant infiltration of the bone marrow. Cancer markers such as prostatic specific antigen (PSA) and breast carcinoma antigen (CA 15–3) may also be helpful. An osteoporotic fracture will be associated with a decreased BMD on different sites of measurement by dual energy X-ray absorptiometry (DXA), although cancer with or without bone metastasis could be also associated with general bone loss.

In breast cancer, oestrogen therapy is usually contraindicated. Tamoxifen, a synthetic anti-oestrogen, is widely used in breast cancer treatment and significantly reduces the risk of recurrence and death when it is used as adjuvant therapy. In premenopausal women, tamoxifen acts as an anti-oestrogen on bone tissue and results in bone loss [12]. In contrast, several studies have shown a prevention of bone loss in postmenopausal breast cancer patients treated by tamoxifen compared with healthy postmenopausal controls, suggesting an oestrogen-like effect on bone despite anti-oestrogenic activity on the breast. The beneficial effects of tamoxifen on BMD in postmenopausal women are more pronounced in late than in early postmenopausal women and more in cancellous than in cortical bone. Love and associates [13] have shown, in a large prospective, double masked, randomised, controlled study, an increased BMD at the spine in breast cancer patients treated with tamoxifen (20 mg/day) compared with a decreased BMD in the placebo group. This effect was related to a decrease in bone turnover as shown by the decrease of serum osteocalcin. Recently, tamoxifen has been shown to reduce bone loss by approximately 50% in patients with an artificial menopause due to adjuvant chemotherapy of breast cancer. The use of a cyclic treatment with risedronate, a new bisphosphonate, results in increased BMD in these women (Figure 1) [14]. Bisphosphonates represent an effective alternative therapy for prevention of bone loss in patients with breast cancer. Bisphosphonates have also been shown to reduce skeletal morbidity (hypercalcaemia, pathological fractures, surgery and radiotherapy on bone) in patients with bone metastases from breast cancer [15, 16] and in patients with multiple myeloma [17].

New compounds are currently being developed, named Selective Oestrogen Receptor Modulators (SERMs) that interact with oestrogen receptor but act as either oestrogen agonists or antagonists depending on tissue and hormonal status. Their mechanism of action is not yet fully understood. Like tamoxifen, SERMs have oestrogen-antagonist effects on

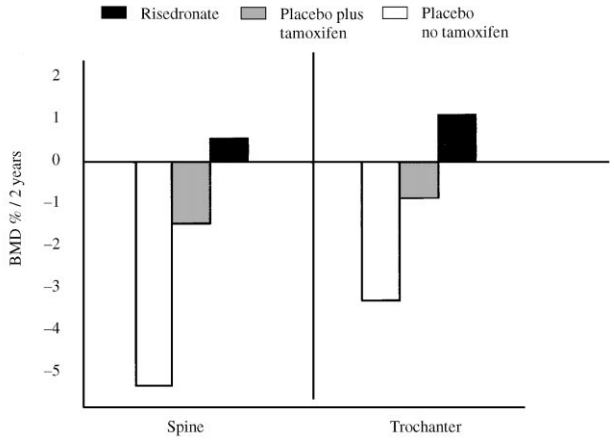

Figure 1. Effects of cyclical risedronate on BMD of the lumbar spine and trochanter. Each column represents the rate of change over the 2 years of treatment. Difference between risedronate and placebo is significant ($P < 0.02$). Adapted from *J Clin Oncol* 1997, 15, 955–962 with permission.

Table 1. *Effects of raloxifen on BMD, serum cholesterol, and uterine endometrium in postmenopausal women compared with placebo.*

	Placebo	Raloxifen treatment 30 mg/day	60 mg/day	150 mg/day
BMD (mean % change from baseline to endpoint)				
Lumbar spine	−0.78	1.28*	1.64*	2.21*
Femoral neck	−1.34	0.55*	1.16*	1.48*
Total body	−0.55	1.26*	1.42*	1.86*
Serum lipids (median % change from baseline to endpoint)				
Total cholesterol	−1.2	−5.2*	−6.4*	−9.7*
LDL-C	−1.0	−6.2*	−10.1*	−14.1*
Total-C: HDL-C	2.4	−1.4	−4.9*	−6.1*
Triglycerides	0	0	3.2	0.5
Endometrial thickness (actual change from baseline to endpoint)				
	0.3 mm	0.2 mm	0.2 mm	0.3 mm

*$P < 0.01$ compared with placebo.

BMD, bone mineral density; LDL-C, low-density lipoprotein cholesterol; total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol. Adapted from *N Engl J Med* 1997, **337**, 1641–1647 permission [21]

breast and oestrogen agonist effects on bone and lipid metabolism. In contrast to tamoxifen, that can be seen as the first generation of SERMs, new SERMS should have little effect on the endometrium. Several compounds have been evaluated clinically. Droloxifen and idoxifen have been used in metastatic breast cancer, but there is still limited information about the effect of these compounds on the uterus and skeleton [18, 19]. Raloxifen has shown beneficial effects in bone turnover and cholesterol level without stimulation of the endometrium in the rat [20]. A double-blind placebo controlled, randomised, phase III study has evaluated the effect of long term treatment with raloxifen (30, 60, or 150 mg/day) in 601 healthy menopausal women. Each dose of raloxifene was associated with a significant increase in BMD at the lumbar spine, hip, and total body whereas those receiving placebo had a decrease in BMD at all sites. Serum total and low density lipoprotein cholesterol concentrations decreased significantly in all raloxifene groups whereas high density lipoprotein cholesterol and triglyceride concentrations remained unchanged. Endometrial thickness was similar in raloxifen and placebo group (Table 1) [21].

Tamoxifen and raloxifen, in oestrogen deficiency, appear to act as oestrogen agonists in bone. SERMs are likely to play an important role in the near future for the prevention of osteoporosis in patients with breast cancer.

CONCLUSION

In conclusion, osteoporosis is a common and multifactorial finding in patients with a history of cancer. In cancer patients with good prognosis who are at high risk of developing osteoporosis, BMD should be assessed by DXA and treatment decisions should be made accordingly. Bisphosphonates and new compounds, such as SERMs, are helpful for improving the management of osteoporosis in those patients.

1. Friedlaender GE, Tross RB, Doganis AC, *et al.* Effects of chemotherapeutic agents on bone. *J Bone Joint Surg* 1984, **66A**, 602–607.
2. Diamond T, Nery L, Hales I. A therapeutic dilemma: suppressive doses of thyroxine significantly reduce bone mineral measurements in both premenopausal and postmenopausal women with thyroid carcinoma. *J Clin Endocrinol Metab* 1990, **72**, 1184–1188.
3. Uzzan B, Campos J, Cucherat M, *et al.* Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. *J Clin Endocrinol Metab* 1996, **81**, 4278–4289.
4. Lukert BP. Glucocorticoid and drug-induced osteoporosis. In Favus MJ. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. Philadelphia, New York, Lippincott-Raven. Third edn, 278–282.
5. Stepan J, Lachman M, Zverina J, *et al.* Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodeling. *J Clin Endocrinol Metab* 1989, **69**, 523–527.
6. Holmes SJ, Whitehouse RW, Clark ST, *et al.* Reduced bone mineral density in men following chemotherapy for Hodgkin's disease. *Br J Cancer* 1994, **70**, 371–375.
7. Daniell HW. Osteoporosis after orchiectomy for prostate cancer. *J Urol* 1997, **157**, 439–444.
8. Redman JR, Bajorunas DR, Wong G, *et al.* Bone mineralization in women following successful treatment of Hodgkin disease. *Am J Med* 1988, **86**, 65–72.
9. Chapman RM, Sutcliffe SB. Protection of ovarian function by oral contraceptives in women receiving chemotherapy for Hodgkin disease. *Blood* 1981, **58**, 849–851.
10. Delmas PD, Hormone replacement therapy in the prevention and treatment of osteoporosis. *Osteoporosis Int* 1997, 7, Suppl. 1, S3–S7.
11. Bruning PF, Pit MJ, de Jong-Bakker M, *et al.* Bone mineral density after adjuvant chemotherapy for premenopausal breast cancer. *Br J Cancer* 1990, **61**, 308–310.
12. Powles TJ, Hickish T, Kanis JA, *et al.* Effect of tamoxifen on bone mineral density measured by dual energy X-Ray absorptiometry in healthy premenopausal and postmenopausal women. *J Clin Oncol* 1996, **14**, 78–84.
13. Love RR, Mazess RB, Barden HS, *et al.* Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med* 1992, **326**, 852–856.
14. Delmas PD, Balena R, Confavreux E, *et al.* Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer: a double blind, placebo-controlled study. *J Clin Oncol* 1997, **15**, 955–962.
15. Hortobagy GN, Theriault RL, Porter L, *et al.* Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastase. *N Engl J Med* 1996, **335**, 1785–1791.
16. Paterson AHG, Powles TJ, Kanis JA, *et al.* Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol* 1993, **11**, 59–65.
17. Berenson JR, Lichtenstein A, Porter L, *et al.* Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 1996, **334**, 488–493.
18. Rauschining W, Pritchard KI. Droloxifen, a new antiestrogen/its role in metastatic breast cancer. *Breast Cancer Res Treat* 1994, **31**, 83–94.
19. Coombes RC, Haynes BP, Dowset M, *et al.* Idoxifen: report of a phase I study in patients with metastatic breast cancer. *Cancer Res* 1995, **55**, 1070–1074.
20. Black LJ, Sato M, Rowley ER, *et al.* Raloxifene (LY 139481 HCL) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. *J Clin Invest* 1994, **93**, 63–69.
21. Delmas PD, Bjarnason NH, Mitlak BH, *et al.* The effects of raloxifene on bone mineral density, serum cholesterol, and uterine endometrium in postmenopausal women. *N Engl J Med* 1997, **337**, 1641–1647.