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General and Supportive Care

Bone health in the elderly cancer patient: A SIOG position paper

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ABSTRACT

More than a third of cancers are diagnosed in people over the age of 75. Androgen deprivation for prostate cancer and aromatase inhibitors in breast cancer accelerate age-related bone loss and increase fracture rates. BMD should be checked by dual energy X-ray absorptiometry at baseline and, dependent on risk, every 12–24 months. Sufficient calcium, vitamin D and exercise are part of primary fracture prevention. Resistance exercise in particular may improve functional activity and bone density. In men at increased fracture risk and women with postmenopausal early breast cancer, antiresorptive treatment is warranted to reduce fracture rate and to increase overall survival in breast cancer. Bone metastases (BM) are common in breast and prostate cancer and lytic bone lesions typical of multiple myeloma. They can cause fractures, pain and spinal cord compression, require surgery or radiation for symptom relief, and lead to hypercalcaemia. Multidisciplinary working with patients and carers can improve quality of life for elderly patients with BM and mitigate the adverse consequences of therapy. Bisphosphonates and other osteoclast inhibitors such as denosumab reduce this morbidity, improve quality of life and reduce pain. Especially in the elderly, attention should be paid to renal function and to risk factors for osteonecrosis with bone-modifying agents. Attention should also be paid to hypocalcaemia risk, which can be considerable in elderly men with metastatic prostate cancer and vitamin D deficiency. We urgently need further research specifically directed at assessing risks and benefits of bone targeted treatments in the growing population of elderly cancer patients.

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Introduction

Bone health and cancer are intimately involved. Most obviously, this is because of bone metastases (BM). Circulating breast and prostate cancer cells have an affinity for the bone tissue and marrow microenvironment which offers sanctuary to cells that may emerge years later from dormancy [1]. Such cells produce factors that increase production of RANKL (receptor activator of nuclear factor kappa ligand) by cells of the osteoblastic lineage, activating osteoclasts and unbalancing bone formation and resorption. As matrix is broken down, bone-derived factors stimulate proliferation of tumour cells and their secretion of osteolytic factors. These interactions contribute to the development of metastases within bone (mostly in the axial skeleton) and elsewhere [2].

Metastases lead to skeletal-related events (SREs) which are usually symptomatic, cause life-altering morbidity, reduce overall survival and increase care costs [3,4]. Diagnosis of BM is generally straightforward but may be confused with benign changes in elderly patients in whom degenerative disease and osteoporosis are common.

A second connection between cancer and bone is that several treatments used to treat hormone-responsive tumours have a deleterious indirect effect on bone turnover, bone mineral density and bone quality. In the elderly in particular, cancer treatment-induced bone loss (CTIBL) is superimposed on physiological bone loss. Osteoporosis, characterised by low bone mass and a deterioration in bone microarchitecture, has a high incidence in older patients, and is strongly associated with fracture risk [5]. Osteoporotic fractures cause the loss of more disability-adjusted life years than any cancer other than that of the lung [6]. The global burden of osteoporosis will rise with the ageing of the world's population, but, at

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the age of 50, the lifetime risk of fracture of the hip, spine or forearm is already 50% in women and 20% in men [7,8].

Classically, osteoporosis is diagnosed by the quantitative assessment of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) and a *T*-score less than −2.5 below peak bone mass. However, since fracture risk is influenced by factors other than bone mass, BMD alone has a relatively low sensitivity [9]. The identification of independent risk factors, including age [10], led to the development of the WHO fracture risk assessment tool (FRAX) [11]. This calculates the 10-year probability of a major osteoporotic fracture or hip fracture alone. However, the FRAX tool has not been validated in a cancer population and substantially underestimates the effects of CTIBL [12].

In addition to BM themselves, and CTIBL, there is increasing evidence that the microenvironment of the bone marrow affects cancer dissemination. Bone modifying agents (BMAs) may therefore directly influence cancer survival [13].

Breast cancer

The median age of those who die of the disease is 68 years [14–16]. Since the number of elderly women is rapidly rising [17], the number of breast cancers and their associated complications, including bone metastases and the adverse effects on bone of systemic therapies, will inevitably increase.

Impact of treatment on bone health

Postmenopausal women in general are at increased risk of low BMD, bone fragility and fracture [18]. The lifetime risk of fracture in women over 50 years is around 40%. Endocrine therapy can lead to further bone loss.

Elderly women with hormone receptor-positive early breast cancer (EBC) are more likely to die of causes unrelated to breast cancer than they are to die from their breast tumour. For this reason, the long-term risks of adjuvant endocrine therapy must be carefully balanced against benefits [19]. Each patient should be assessed in relation to her individual likelihood of adverse effects and benefits from a particular therapy. Classical risk factors for fracture include age, personal and family history of hip fragility fractures, comorbidities, corticosteroids, tobacco and alcohol.

Aromatase inhibitors (AIs) increase OS in controlled trials against tamoxifen; and the adverse effects of AIs on bone have to be seen in the context of the increased risk of other adverse events (AEs) with tamoxifen. That said, AI therapy is associated with an average 2% loss of lumbar spine BMD per year [20]. This compares with a mean 0.5% annual loss in elderly women in general; and there is evidence that the effects of AIs on cortical bone and on bone strength are largely underestimated by DXA [21].

The absolute risk of fracture in women treated with an AI for 5 years ranges from 1% to 18%. The latter figure, derived from a database of women with 4–5 years of therapy [22], is supported by data from the placebo group in ABCSG-18 showing a fracture rate of 9.6% after three years and 26% after seven years. When letrozole was compared against tamoxifen in the BIG1-98 study, the fracture rates were 8.6 vs 5.8%. Similar adverse effects are seen with exemestane.

Risk of fracture is 2–4 times higher in women treated with adjuvant AIs than with tamoxifen or placebo. The increased risk is independent of type of AI and, with the exception of ABCSG-18, where fracture incidence was the primary endpoint, has been underestimated because fractures were only reported as AEs.

In elderly women, fractures are associated with five times greater than expected mortality over three months [23,24]. This may in part reflect underlying frailty, but preventing bone loss should be an important aspect of supportive care. Even so, the perceived lack of importance of skeletal outcomes is suggested by the fact that only 4 of 11 RCTs included in a major review had a subprotocol looking specifically at effects on bone [19]. Our understanding of how age interacts with risk to bone is limited because the mean age of patients was below 65 years in all the RCTs considered. To inform management, we urgently need more research into risks and benefits in the growing population of elderly breast cancer patients.

Bisphosphonates (BPs) inhibit osteoclast-mediated bone resorption and prevent treatment induced bone loss, including that caused by AIs. The five-year results of the ZO-FAST study in postmenopausal breast cancer patients receiving 2.5 mg/day letrozole found that immediate initiation of zoledronic acid 4 mg q six months increased both lumbar spine and total hip BMD relative to baseline while delayed treatment was associated with a progressive reduction in BMD [25]. Immediate treatment with ZA also improved DFS.

Denosumab specifically inhibits RANK ligand and hence osteoclast formation and function. It is a highly effective treatment for AI induced bone loss [26,27]. The ABCSG-18 trial, which randomised postmenopausal women on AIs to denosumab 60 mg Q6M or placebo, found that active treatment led to similar increases in BMD (lumbar spine and femoral neck) over three years [27]. More importantly, the risk of first clinical fracture (the primary endpoint) was also substantially reduced (HR 0.50) relative to placebo. Five years following randomisation, 15% of placebo patients but little over 5% of denosumab-treated patients had experienced a fracture. A significant protective effect was seen both in women with a baseline *T* score of less than −1 and in those with a *T* score of −1 or more; and the benefit to women aged 70 and older was similar to that in younger patients. These new findings will have to be considered when updating guidelines for the prevention of AI-induced bone loss, especially given that denosumab was not associated with additional toxicity. In particular, there was no concern over osteonecrosis of the jaw (ONJ) or atypical femoral fractures.

Important additional evidence is provided by the recent Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of data from postmenopausal breast cancer patients showing that adjuvant ZA and clodronate could reduce recurrence rate and prolong survival [28]. Overall, BPs had no significant effect on breast cancer recurrence (rate ratio 0.94) and the effect on breast cancer mortality, though significant, was small (RR = 0.91). However, in postmenopausal women, clinically important benefits were seen with improvements in overall breast cancer recurrence (RR = 0.86), distant recurrence at any site (RR = 0.82), bone recurrence (RR = 0.72) and breast cancer-specific mortality (RR = 0.82). These benefits were most pronounced in older women although relatively few women over 70 were included in the trials. Initial results from ABCSG-18 also suggest a benefit on disease recurrence with an absolute decrease in events of 2.1% at five years compared to placebo. Follow-up is too short to see effects on mortality [29].

This protective effect may arise because products of increased bone turnover attract cancer cells to bone and stimulate their growth, although it is not clear why this antitumor effect is only observed in postmenopausal women. Some BPs, and maybe denosumab, maintain the dormant state of cells that have metastasized to marrow, reducing the likelihood of dissemination.

Current guidelines for preventing bone loss in postmenopausal and older women with breast cancer

The most recent ESMO algorithm suggests that patients having adjuvant endocrine treatment should be managed according to risk [30]. Patients with a *T*-score of greater than −2 and no additional risk factors should exercise and receive calcium and vitamin D,

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