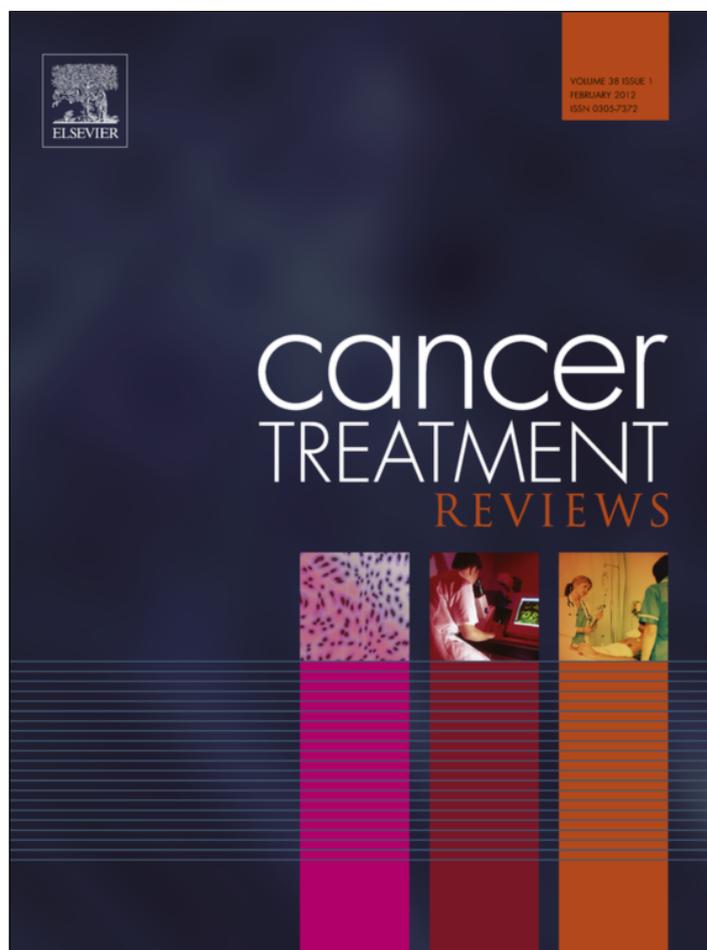


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General and Supportive Care

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

J.J. Body^{a,*}, E. Terpos^b, B. Tombal^c, P. Hadji^d, A. Arif^e, A. Young^f, M. Aapro^g, R. Coleman^h^a CHU Brugmann, Université Libre de Bruxelles (ULB), Brussels, Belgium^b Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece^c Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium^d Krankenhaus Nordwest, Department of Bone Oncology, Endocrinology and Reproductive Medicine, Philipps-University of Marburg, Frankfurt, Germany^e University Hospitals Coventry and Warwickshire, UK^f Warwick Medical School, University of Warwick, England, UK^g Breast Center, Multidisciplinary Oncology Institute, Clinique de Genolier, Switzerland^h Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

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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

* Corresponding author at: CHU Brugmann, Dept of Medicine, Place Van Gehuchten, 1020 Brussels, Belgium.

E-mail address: jean-jacques.body@chu-brugmann.be (J.J. Body).

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 sub-protocol 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,

with risks and BMD monitored every one–two years. If the *T*-score is less than -2 , or there are two or more risk factors (which include age over 65 year, smoking, family history and steroid use), patients should receive the same advice and supplements plus BPs (ZA, alendronate, risedronate or ibandronate) or denosumab.

The results of ABCSG-18 and the EBCTCG meta-analysis, which compared outcomes in those who were allocated adjuvant BPs of any type or duration versus those who were not, suggest that guidelines for prevention have to be reviewed. The improvements in both DFS and OS in early breast cancer in older patients with low levels of reproductive hormones are now clear. At least for postmenopausal breast cancer, there is a case for giving antiresorptive therapy to all patients being treated with AIs, independent of *T*-score. Further, given the steeply increased risk of hip fractures after the age of 70–75, prevention of bone loss with BPs or denosumab should probably be recommended for all patients aged over 75 [31].

There are insufficient data with osteoporosis schedules of alendronate or risedronate to evaluate their potential for metastasis prevention. The first results of ABCSG-18 showing prolonged DFS in denosumab-treated women are encouraging but further follow-up is needed before recommending denosumab for that specific purpose.

Prostate cancer and bone health

Men also experience a steady loss of BMD with aging, and one in five men over 50 suffers an osteoporotic fracture. Almost 30% of all hip fractures are in men, and the associated mortality is substantially higher than in women [32]. The American College of Preventive Medicine recommends that men aged 70 and above are screened for osteoporosis using DXA [33]. In the United States, 57% of prostate cancer diagnoses were in men aged 65 and over [16] and the median age of death from the disease is 80 [34]. Thus, bone health is an important, and under-recognised issue in these older men.

Androgen deprivation and bone loss

Androgen deprivation therapy (ADT), by means of orchiectomy or LHRH analogues is the cornerstone of treatment in prostate cancer – both to prevent and to treat metastatic disease – but has important adverse effects on bone health [20]. Levels of urinary N-telopeptide, a marker of bone resorption, are elevated even six months after the start of ADT. According to DXA of the hip and lumbar spine, men treated with LHRH agonists lose 1–5% of BMD within the first year. A matched-cohort study of almost twenty thousand men found that the risk of fragility fracture (all sites) was 17.2% for those on ADT (mean duration 6.5 years) compared with 12.7% among men not on ADT (HR 1.65) [35]. Hospitalisation rates were 8% vs 5.7% respectively. Increasing age was an independent risk factor for fractures, which in most cases were managed in an ambulatory setting. Even so, according to US data, fracture in prostate cancer more than doubles mortality [36].

Shahinian et al. looked at outcome among men aged 66 and older who had had either orchiectomy or LHRH agonists and were included in SEER-Medicare databases [37]. Of men on ADT, 5.2% experienced a fracture requiring hospitalisation within five years of diagnosis, while this was true of only 2.4% of those not on ADT. Fracture risk increased with treatment duration. There were also significant interactions such that the relative risk of ADT tended to decline with age. The RR with ADT also fell with increasing comorbidity. The number needed to harm (any fracture 12–60 months after diagnosis) was 28 for any use of LHRH agent.

Corticosteroids are extensively used with both chemotherapy and ADT [38] and may be given to patients with no or minimal metastatic disease [39]. Concern has been crystallized by the recent introduction of the androgen synthesis inhibitor abiraterone for castration-resistant prostate cancer (CRPC), because of its impact on endogenous cortisone production. Abiraterone must be combined with 10 mg prednisone. Abiraterone and other new agents significantly extend overall survival in CRPC, so that prolonged exposure to steroids may be expected, potentially increasing the risk of osteoporotic fracture. Because of its favourable toxicity profile, abiraterone is especially suited to elderly patients who are not good candidates for chemotherapy. There is limited information on the possible acceleration of BMD loss with abiraterone plus prednisone but a single institution study found loss of muscle and visceral fat [40].

Recommendations for monitoring and treatment

ZA, alendronate and denosumab at osteoporosis doses prevent ADT-induced bone loss [41,42]. Denosumab also prevents ADT-induced vertebral fractures: in Smith et al., the rate of fractures evident at two years using morphometry on sequential X-rays was 3.3% with placebo and 1% with denosumab (RR 0.31). Overall rates of AEs were similar.

For the prevention of osteoporosis-related fracture in ADT-treated patients without metastases, EAU guidelines suggest treating osteoporotic patients, ie those with a DXA *T*-score of minus 2.5 or more, with denosumab or bisphosphonates. The NCCN guidelines recommend zoledronic acid (5 mg iv annually) alendronate (oral 70 mg weekly) or denosumab (60 mg sc every six months) for men with a 10 year probability of hip fracture of 3% or more, or a 20% or greater probability (on FRAX) of a major osteoporosis-related fracture. With denosumab, in contrast to ZA, there is no need for dose adjustment in the case of renal impairment.

Despite the prevalence of the problem in prostate cancer, guidelines for this indication have received less attention. However, they should probably be broadly similar to those in breast cancer. Men aged over 75 years should receive antiresorptive agents at doses used to prevent osteoporosis.

Elderly men are more likely than their younger counterparts to require dose adjustment for renal impairment. They are also at greater risk of hypocalcaemia and vitamin D deficiency, and, since dental disease and extraction is more frequent, of treatment-related ONJ (see Table 1).

Management of bone metastases and the prevention of SREs

Management of patients with bone metastases (BM) requires a multidisciplinary team (MDT) including specialists in symptom control. Treatment is generally palliative. External beam radiotherapy [43], endocrine treatments, chemotherapy, targeted therapies, radioisotopes and surgery are options. Complementing these treatments are the BPs and denosumab which the controlled trials reviewed below have shown to reduce skeletal morbidity.

Efficacy of bone modifying agents

Although antiresorptive therapies are especially important for elderly cancer patients, they are typically underutilised [44]. Such underuse may be more detrimental in elderly than in younger patients because of the high fracture risk conferred by physiologic decreases in BMD and age-related increases in vertebral and (to an even greater extent) non-vertebral fracture rate. Special consideration should be given to elderly patients with renal impairment and those taking concomitant medications. Careful monitoring of

Table 1

General recommendations on use of bone modifying agents.

- Evaluate creatinine clearance
- Correct any pre-existing hypocalcaemia before starting bone modifying agents
- Monitor serum calcium level, especially during the first six months of treatment
- Use of calcium and vitamin D supplements in all patients except those who are hypercalcaemic
- Adjust lifestyle to include weight-bearing exercise, smoking cessation and limiting alcohol intake
- Pause bone modifying agents in patients who develop symptomatic hypocalcaemia until normal level has been restored
- Attend to oral hygiene and avoid invasive dental procedures

comorbidities is essential to ensure safety, especially during chemotherapy [45].

Compared against ZA 4 mg Q4W in BP-naive patients with BM, denosumab 120 mg Q4W was statistically superior in reducing overall risk of SRE, and in delaying time to first SRE, the development of moderate/severe pain and worsening of health-related quality of life [46]. However, both treatments remain appropriate and the choice of agent should be based on individual factors and side effect profile, as well as the very different cost implications of the two treatments now that ZA is generic [47].

Although BPs or denosumab should be started as soon as BM are diagnosed in order to delay the first SRE and reduce complications, their use in women with depleted calcium and vitamin D increases risk of severe hypocalcaemia. Given the prevalence of vitamin D deficiency in the elderly, assessment of calcium and vitamin D status, rapid replacement if deficient, and supplementation during treatment, are strongly recommended.

With regard to BPs in the elderly, the assessment of serum creatinine and GFR is important since renal impairment may require dose adjustment of zoledronic acid. Denosumab is an alternative, since this agent is not renally cleared, but hypocalcaemia is more frequent in patients with impaired renal function. ASCO and other guidelines state that BPs should be continued until decline in general performance status [48,49]. However, interrupting ZA or reducing infusion frequency is often considered when bone disease is well-controlled and the risk of SREs, especially fractures, is considered low. Continued treatment, possibly with intensive ZA, as discussed below, is recommended for patients with progression of BM, a recent SRE and perhaps also those with elevated resorption markers. But we lack a predictive tool for SREs analogous to the FRAX score for fractures.

Several trials have investigated the schedule of BP treatment. Two studies (ZOOM and OPTIMIZE) suggested that the efficacy of 3 monthly and monthly administration of ZA is similar after about a year of monthly treatment to “load” the skeleton [50,51].

More recently, the CALGB 70604 (Alliance) trial, which randomized patients with BM from a range of different primary tumour types to ZA on a monthly or 3 monthly schedule from the outset of treatment for two years, showed the non-inferiority of less frequent administration [52]. In both arms, 29% of patients developed ≥ 1 SRE. The proportion of patients with renal dysfunction was 1.2% versus 0.6% for monthly and three-monthly schedules, and ONJ was experienced by 2% vs 1%. Data from trial 70604 are not fully published and there is some concern about higher rates of fractures and surgical interventions in the q 3 month arm. However, when taken together, the evidence suggests that 3 monthly administration of ZA is certainly reasonable after a period of monthly treatment, the duration of which should depend on the estimated risk of bone complications.

Unlike BPs, denosumab is not stored in bone and interruption is probably not without risk [53]. A rebound effect is plausible [54],

and continuous monthly therapy for metastatic bone disease should be recommended until we have the results of ongoing studies of less frequent administration after one year of monthly therapy. When stopping denosumab in patients with metastatic bone disease, until more data are available, it is probably appropriate to switch to a less intense schedule of iv BP using an infusion every three months or to oral clodronate. However, this recommendation is not supported so far by prospective clinical trials.

Risk of adverse events

Both BPs and denosumab are generally well-tolerated. However, ZA is associated with more episodes of acute phase response symptoms and renal dysfunction [55]. Particular attention should be paid to the potential renal toxicity of ZA. The product label advocates stepwise dose reductions when baseline creatinine clearance is 30–60 ml/min, and ZA is not recommended in patients with severe renal deterioration or those taking nephrotoxic medications.

The impact of BPs on renal function is likely to be more clinically relevant in elderly patients. On the other hand, hypocalcaemia is more frequent and more likely to be symptomatic with denosumab, especially in patients with decreased renal function. Physicians should strongly advise patients to take calcium and vitamin D supplements and regularly monitor serum calcium levels to reduce the risk of hypocalcaemia [56].

The most important AE associated with frequent and prolonged administration of potent inhibitors of bone resorption is ONJ [57,58]. ONJ is much more common (around 1–2% per year on treatment) when intravenous BPs or denosumab 120 mg are administered monthly for control of metastases than with less intensive use for preservation of bone mass or treatment of established osteoporosis (risk <0.01 to $<0.1\%$ per year on treatment with oral BPs or yearly 5 mg ZA or 6-monthly denosumab 60 mg).

In the pre-specified analysis of denosumab trials, the incidence of ONJ did not differ significantly between denosumab-treated patients (incidence 1.8%) and ZA (1.3%) [59]. Most patients with confirmed ONJ had a history of tooth extraction (62%), poor oral hygiene and/or use of a dental appliance. ONJ is thus more likely to occur in elderly patients due to the higher prevalence of dental problems. Before ZA or denosumab is initiated, patients should have preventive dentistry and be advised on oral hygiene. If possible, patients should avoid extractions during therapy. Evidence is insufficient to conclude that discontinuing ZA or denosumab facilitates the resolution of ONJ [48,49] (see Table 2).

Multiple myeloma

In the US, 62% of cases of multiple myeloma (MM) and 77% of deaths from the disease are in people aged 65 years and above [60]. Geriatric and functional assessment inform decisions about the appropriate intensity of treatment and choice of agent. The International Myeloma Working Group has recently used pooled trial data to develop a frailty score based on age, comorbidities, and cognitive and physical status [61]. Dividing patients into those who are fit, intermediate or frail identifies groups which differ in three-year overall survival (84% vs 76% vs 57% in the three groups respectively) independently of ISS stage, chromosome abnormalities and type of treatment. Declining fitness also relates to increased likelihood of treatment toxicity (rate of grade 3 or greater non-haematological AEs at one year 22% vs 26% vs 34% in the three groups) and treatment discontinuation at one year (17% vs 21% vs 31%).

MM may present as diffuse osteoporosis, which can cause diagnostic problems in an elderly population where prevalence of

Table 2
Recommendations (with grades of evidence) for managing bone metastases in breast and prostate cancer, including in the elderly. Based on Coleman R and von Poznak C (2015) [76].

Use an osteoclast inhibitor to reduce skeletal complications (Grade 1A).
Before treatment: <ul style="list-style-type: none"> • perform a dental exam and necessary dentistry • correct existing hypocalcaemia and/or vitamin D deficiency • counsel patients on adequate intake of calcium and vitamin D
Choice of agent and regimen: For most patients, denosumab (120 mg q 4 weeks) is preferred, based on delayed first and subsequent SREs vs ZA (Grade 2B). A BP is acceptable and ZA preferred based on efficacy and short infusion (Grade 2B). Pamidronate is also reasonable as are oral ibandronate or clodronate for patients at risk of renal toxicity or preferring oral route. The approved schedule for ZA is 4 mg iv q 3–4 weeks, adjusted for creatinine clearance. However, data in breast and prostate cancer support a longer dosing interval for selected patients. For most patients who are not candidates for denosumab and whose bone metastases are neither highly symptomatic nor extensive, we suggest ZA every three months, especially in elderly patients (Grade 2B). At least initially, monthly dosing is preferable for patients with extensive or highly symptomatic bone metastases. The optimal duration and frequency of ZA infusion deserves further study; until then, administration schedule should be adapted to the patient. For patients who experience an SRE while on osteoclast-inhibiting and anti-cancer therapy, continue osteoclast inhibition (Grade 2C).

osteoporosis is common. It is associated with a range of complications related to bone destruction, anaemia and renal and immunological impairment. All adversely affect quality of life and may reduce life expectancy. In the present paper, we focus on the preservation of bone health in the elderly MM patient according to recent guidelines from the European Myeloma Network (EMN) [62].

Osteolytic bone disease, found in up to 80% of patients at diagnosis, leads to the full range of SREs. Recommendations for its detection and management are shown in Table 3. Although conventional radiography has been standard for the detection of lytic lesions in MM, whole-body, multi-detector, low dose computed tomography (WBLD-CT) is more sensitive, takes no more than 2 min to conduct, detects more lesions, and is better able to identify areas at risk of fracture. Although its prognostic value remains to be determined, evidence suggests that WBLD-CT in this setting is superior to conventional radiography. Hence the European Myeloma Network has suggested that WBLD-CT is the method of choice for the diagnosis of lytic disease in MM.

Compliance has an important role since strict adherence to dosing recommendations is required for BPs to effectively reduce risk of SREs [63]. Intravenous administration (which can be organised at home) is the preferred route. These considerations may be particularly relevant to the elderly MM patient.

Persistence with bone-related therapy

Available data are from breast cancer. Retrospective analysis of a major German database identified more than a thousand patients with BM given their first prescription for BPs (73% iv) [64]. After one year, 35% of patients on iv and 46% of those on oral therapy had discontinued. Persistence was therefore low and likely to impair clinical outcome. In the context of the elderly, it is worth noting that women aged over 70 years were less likely to discontinue than women younger than 50. This positive effect of age on persistence has recently been confirmed in a second German study [65]. The rate of discontinuation (ie more than 90 days without treatment) among breast cancer patients with bone metastases who had begun BP treatment between 1994 and 2013 was 44% in those younger than 70 but only 35% in older patients.

Currently, no data on persistence with denosumab in women with breast cancer have been reported. In women with osteoporosis, persistence with oral and i.v. bisphosphonates is low while that with denosumab is higher. After two years of follow-up the proportion of patients still on treatment was 39.8% for denosumab, 24.8% for iv ibandronate, and 21.2% for iv zoledronic acid [66].

A nursing perspective

Nurses are well placed to recognise symptoms such as pain and reduced mobility suggestive of skeletal events, can identify the educational and social needs of patients, family and carers [67,68] and provide emotional support [69]. Further roles include the monitoring of side-effects and therapeutic outcomes, and the co-ordination of care which may involve specialists in geriatrics and palliation in both the hospital and the community [70].

Assessing the patient

Bone pain is a cardinal symptom and should be assessed according to location, quality, radiation, duration, intensity, aggravating and ameliorating factors and the efficacy or otherwise of analgesics. Metastatic bone pain is often described as constant and dull with greater intensity at night and on weight bearing. Decreased movement, areas of tenderness, oedema or abnormal positioning should be noted [71,72].

Self-management of cancer-related pain is key for many elderly patients living with BM and nurses are best placed to offer coaching and psychoeducational interventions within the framework of self-care [73,74].

The possibility of malignant spinal cord compression (MSCC) necessitates enquiry about numbness, tingling or coolness in the hands, feet, arms, trunk, legs, fingers and toes [75]. The patient should be asked about bowel and bladder function to identify any injury to the autonomic nerves. The diagnosis of MSCC can cause major psychological distress for patients and their families and nurses need to be aware of the psychological support required [71,72]. Nurses can also contribute to an early diagnosis of SCC, often the best chance to avoid dramatic, irreversible complications.

Management

In the case of pathological fracture, the objectives are pain relief, skeletal stabilisation, preservation or restoration of function and quality of life, and local tumour control. This may be through surgery, but splints and braces are helpful if this is precluded by comorbidities [69,70,74].

Nurses should be aware of all drugs promoting hypercalcaemia and preparations containing calcium, should be stopped. The patient and their family are encouraged to recognise and report symptoms of hypercalcaemia to their key contact [71].

Intravenous bisphosphonate (BP) therapy is delivered by nurses, who should be aware of the adverse event profiles of different agents. The most frequent side effects are acute flu-like symp-

Table 3
European Myeloma Network recommendations (2015) for the management of bone-related complications [62]. Evidence is rated according to the GRADE system.^a

	General recommendations	Considerations particularly relevant to the elderly
Detection	Whole-body low-dose CT (WBLD-CT) is the new standard for detecting lytic lesions (1A). Use conventional radiography if WBLD-CT not available	WBLD-CT requires less than 2 min and so is especially suited to the elderly
Treatment	<p>Bone disease at diagnosis: Treat with zoledronic acid (ZA) or pamidronate (1A)</p> <p>ZA dose is 4 mg (adjusted to renal function) q3–4 weeks by 15 min iv infusion</p> <p>Pamidronate 90 mg, iv, over 2–4 h infusion, q3–4 weeks</p> <p>For newly-diagnosed pts, treatment has to be given continuously; if the patient has achieved vgPR or CR, 12–24 months of BP is recommended. At disease progression, restart BP</p> <p>Symptomatic pts without lytic lesions on conventional radiography may benefit from ZA (1B) but benefit not clear for pts with no bone involvement on CT or MRI</p> <p>Asymptomatic pts: BPs not recommended (1A)</p> <p>Denosumab not yet licensed for MM though phase III trial data are expected; it can be used in cases of hypercalcaemia of malignancy</p>	<p>Closely monitor renal function, serum electrolytes, urinary albumin. For both ZA and pamidronate, Cr Cl needs to be >30 ml/min</p> <p>ZA: in pts with renal impairment (<60 ml/min), reduce dose according to sMPC</p> <p>When Cr Cl < 30, ZA is not recommended</p> <p>Pamidronate: With CrCl of 30–60 ml/min, use standard dose (90 mg) over 4 h. When Cr Cl < 30, pamidronate is not recommended</p> <p>Discontinue BP if renal function deteriorates until CrCl returns to within 10% of base-line (grade 1B). Pts on chronic dialysis without possibility of renal failure reversal should also receive monthly BPs (grade 2C) but need close monitoring due to high risk of hypocalcaemia. In all other pts on dialysis, avoid BPs until they are independent of dialysis and Cr Cl has returned to >30 mL/min (grade 2C)</p> <p>All pts taking BPs should have daily supplements of 600 mg calcium and 800 IU vitamin D3 (1A)</p>
Prevention of ONJ		<p>Thorough dental exam and resolve all major problems prior to starting treatment (2C)</p> <p>If ONJ occurs, discontinue BPs; resume treatment at physician's discretion if condition heals</p>

^a Grading of Recommendations, Assessment, Development and Evaluation.

toms after initial exposure and subsequent nausea/vomiting, fever, headache and lower leg oedema. These are managed by analgesics and reactive antiemetics. Since BPs are eliminated by the kidney, renal function must be carefully monitored, especially with ZA in patients with reduced kidney function [77,78]. To avoid the risk of ONJ, nurses should impress on the patient the need for good oral hygiene and for any dental treatment to be completed before starting therapy [79].

Denosumab is not cleared by the kidneys and dose adjustment is not required but hypocalcaemia is a risk in patients with low creatinine clearance. Nurses can administer it as a subcutaneous injection in an outpatient setting. Hypocalcaemia occurs more commonly than after ZA and therefore calcium and vitamin D supplements are recommended [79–81]. Nurses play a key role in monitoring elderly patients' compliance.

Resistance exercise is an emerging area of interest in which nurses, exercise physiologist and physiotherapists are ideally placed to support patients with BM. Evidence suggests that appropriately designed and supervised resistance exercise may be safe and well tolerated by cancer patients with BM; and the intervention may lead to improved functional ability, physical activity, higher bone density, lean mass and better quality of life [82,83].

Real-time monitoring of patients from their homes, triggering automatic triage and response from the nurse specialist where appropriate, is likely to prove the best means of optimising care for patients with BM (see Table 4).

Discussion

Preserving bone health is of great and growing importance. Tumours of the breast and prostate and multiple myeloma frequently metastasise to bone, inducing severe pain and other SREs, and impairing quality of life. This is also true of lung cancer, which has recently been considered elsewhere [84] and is not included in this paper. The advent of bone-targeted agents such as the potent BPs and denosumab has increased our ability to mitigate the consequences of BM by reducing the rate of pathological fractures, severe pain and hypercalcaemia.

Table 4

Recommendations for nursing care as part of the multidisciplinary management of elderly patients with bone metastases.

- Each patient has one key contact specialist who can be a specialist nurse
- Timed and targeted information should be offered to the patient and their carer
- Ensure each patient is listened to and their concerns documented and acted upon
- Systematic monitoring and holistic assessment of patients at risk of and with bone metastases should be the responsibility of the extended MDT, often coordinated by the nurse specialist
- Patients should choose the approach to monitoring and assessment
- Actions by nurse specialists should be communicated to the MDT

A second factor is that the hormonal manipulations used to treat breast and prostate cancer upset normal bone remodelling and themselves increase bone loss and osteoporosis, with the attendant risk of fractures. These events not only impair quality of life in long-term cancer survivors but also contribute to mortality.

Elderly patients carry the bulk of the cancer burden. Effective treatment is more likely to be complicated by comorbidities and decline in organ function. And, in the context of bone health, the effects of cancer and of its treatment are superimposed – in both men and women – on normal, age-related reductions in BMD. These considerations prompted the convening of an expert SIOG panel. Given the lack of randomised controlled trial data relating to specifically to the elderly, its recommendations are a summary of current knowledge and a basis for further discussion.

Declaration of interest

R Coleman has declared research funding from Amgen and Bayer.

JJ Body has declared funding from Amgen for consultancy and lecture fees. E Terpos has declared honoraria, research grants and travel expenses from Amgen and honoraria from Novartis.

P Hadji has declared funding from Amgen and Novartis for research, lectures and congress support.

A Young has declared none related to bone protection in cancer patients but over the past two years she had received the following honoraria for talks given; honorarium for 1 advisory Board from MSD Global, honorarium for 1 advisory board from Helsinn Europe, educational grant for clinical trial and Honoraria for talks given from Bayer UK and Global, honoraria for talks given; expert committee expenses from Leo Pharma and honoraria for 2 advisory boards from Amgen.

A Arif has no conflicts of interest to declare.

M Aapro is/was a consultant for Amgen, BMS, Celgene, Clinigen, Eisai, Genomic Health, GSK, Helsinn, Hospira, Jnj, Novartis, Merck, Merck Serono, Mundipharma, Pfizer, Pierre Fabre, Roche, Sandoz, Tesaro, Teva, Vifor and has received honoraria for lectures at symposia of Amgen, Bayer Schering, Cephalon, Chugai, Eisai, Genomic Health, GSK, Helsinn, Hospira, Ipsen, Jnj OrthoBiotech, Kyowa Hakko Kirin, Merck, Merck Serono, Mundipharma, Novartis, Pfizer, Pierre Fabre, Roche, Sandoz, Sanofi, Tesaro, Taiho, Teva, Vifor.

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