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REVIEW-THEMED ISSUE

The skeletal impact of cancer therapies

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Abstract

Both cancer and therapies used in the treatment of cancer can have significant deleterious effects on the skeleton, increasing the risks for both bone loss and fracture development. While advancements in cancer therapies have resulted in enhanced cancer survivorship for patients with many types of malignancies, it is increasingly recognized that efforts to reduce bone loss and limit fractures must be considered for nearly all patients undergoing cancer therapy in order to diminish the anticipated future skeletal consequences. To date, most studies examining the impact of cancer therapies on skeletal outcomes have focused on endocrine-associated cancers of the breast and prostate, with more recent advances in our understanding of bone loss and fracture risk in other malignancies. Pharmacologic efforts to limit the adverse effects of cancer therapies on bone have nearly universally employed anti-resorptive approaches, although studies have frequently relied on surrogate outcomes such as changes in bone mineral density or bone turnover markers, rather than on fractures or other skeletal-related events, as primary study endpoints. Compounding current deficiencies for the provision of optimal care is the recognition that despite clearly written and straightforward society-based guidelines, vulnerable eligible patients are very often neither identified nor provided with appropriate treatments to limit the skeletal impact of their cancer therapies.

KEYWORDS

androgen deprivation therapy, aromatase inhibitor, bone loss, breast cancer, myeloma, prostate cancer

1 | INTRODUCTION

Even before the initiation of cancer treatment therapies, patients with cancer are at increased risk for accelerated bone loss, as evidenced by lower bone mineral density in cancer patients relative to subjects without cancer, regardless of cancer type.[1] Adding to this underlying skeletal insult is the further damage that results from many cancer therapies. Thus, bone loss in patients with cancer reflects both the effects of the cancer itself, as well as the skeletal response to therapies currently used to treat cancer including a wide range of chemotherapeutics, as well as agents such as glucocorticoids, aromatase inhibitors (AIs) and androgen deprivation therapies. In addition, bone is also a very common site of cancer metastasis, with tumour cells exerting both direct and indirect effects on bone cells to cause systemic as well as localized bone loss. When viewed through the prism of the increased survivorship now commonly seen in patients with many types of malignancies, efforts to limit bone loss and fractures that can significantly diminish quality of life, have become increasingly important for the care of cancer patients.

This paper will focus on currently used cancer therapies, the impact of these therapies on the skeleton, and available data for limiting bone loss and fractures in cancer patients treated with these therapies. Given that the majority of work to date has focused on patients with breast and prostate cancers, this review will emphasize those cancers, but will also include discussion of more general treatments such as glucocorticoids, as well as data on cancer therapies for haematologic malignancies.

2 | BREAST CANCER

Age-associated declines in sex steroid levels (oestradiol in women; testosterone which undergoes aromatization to oestradiol in men) underlie normal age-associated bone loss in both women and men.[2] In the most common hormonally-associated malignancies (breast cancer in women and prostate cancer in men), however, therapeutic approaches frequently are focused on severely reducing sex steroid levels and/or antagonizing their effects at the receptor level. Collectively, these interventions have the potential to induce additional bone loss above and beyond that already occurring in individuals who are frequently of advanced age at the time of cancer diagnosis. Further, there is good evidence that despite the well-recognized risks of bone loss and fracture seen with hormonal therapy both in patients with breast and prostate cancers and despite well-established guidelines put forth by professional societies, systematic skeletal health evaluations are only infrequently performed and vulnerable patients are thus left untreated.[3]

2.1 | Breast cancer in premenopausal women

In premenopausal women receiving chemotherapy for breast cancer, menopausal onset occurs on average roughly 10 years earlier than would occur naturally, usually as a result of chemotherapy-induced ovarian failure.[4] With advances in lifespan from time of diagnosis resulting from both therapeutic advances and earlier detection, many premenopausal women diagnosed with breast cancer now endure prolonged skeletal insults from a combination of hormonal therapies, chemotherapy and glucocorticoids that are frequently prescribed to combat nausea.

2.1.1 | Aromatase inhibitor therapies

Aromatase inhibitors lower endogenous oestradiol levels via inhibition of the enzyme aromatase. In premenopausal women, physiologic oestradiol levels regulate bone mass by attenuating receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) signalling via the RANK receptor,[5] thereby inhibiting osteoclast formation and reducing bone turnover. Sustained reductions in oestradiol levels, as occur with prolonged aromatase inhibitor treatment, lead to rapid bone loss primarily due to increased osteoclast-mediated bone resorption and result in marked increases in cortical porosity and trabecular deterioration,[6] factors which ultimately increase fracture risk.[7] In premenopausal women in whom endogenous estrogen levels have not been (or cannot be) accurately determined (such as women in the perimenopause and those with presumed chemotherapy-induced ovarian failure), AI treatment as monotherapy is not recommended. Rather, in such women, the use of an AI with either concomitant oophorectomy or GnRH agonist therapy is considered standard of care.

In order to evaluate whether treatment with the potent intravenous bisphosphonate zoledronic acid provided every six months is able to limit bone loss in premenopausal women treated for breast cancer, the ABCSG-12 investigators performed a sub-study of a large phase 3 trial in which subjects received a gonadotropin-releasing hormone agonist (to indirectly suppress endogenous estrogen production) in addition to treatment with either tamoxifen or an aromatase inhibitor.[8] As assessed by dual-energy x-ray absorptiometry (DXA), endocrine therapy for 36 months reduced bone mineral density (BMD) at the lumbar spine by −11.3% and hip by −7.3%. Whereas women treated with tamoxifen lost an average of −9.0% at the lumbar spine, subjects treated with an aromatase inhibitor suffered even greater reductions in BMD (−13.6%). In comparison, women who received either endocrine therapy but who were simultaneously treated with zoledronic acid showed no BMD differences from baseline at 36 months. Other studies have shown comparable effects for a protective skeletal role with zoledronic acid treatment in premenopausal women receiving neoadjuvant or adjuvant chemotherapies for breast cancer.[9] Premenopausal women who experience return of menses after completion of adjuvant chemotherapy may regain some of the bone mineral density lost during treatment.[10]

2.1.2 | Selective estrogen receptor modulators

Tamoxifen, a selective estrogen receptor modulator (SERM), functions as a partial estrogen receptor antagonist on breast tissue, a property which allows it to be used for treatment in women with estrogen receptor positive breast cancers or as prophylactic therapy in women at high risk of breast cancer. However, tamoxifen also functions as a partial agonist/antagonist on estrogen receptors in bone. Thus, in premenopausal women treated with tamoxifen as prophylaxis against the development of breast cancer, and premenopausal women who do not undergo menopause during adjuvant chemotherapy treatment, tamoxifen has been associated with bone loss.[11]

2.2 | Breast cancer in postmenopausal women

The majority of women diagnosed with breast cancer are postmenopausal. In addition to the skeletal insult imposed by menopause, breast cancer therapies are now well recognized as agents which further increase bone loss and fracture risk.

2.2.1 | SERMs

Unlike in premenopausal women in whom tamoxifen functions as an antagonist at the estrogen receptor to induce bone loss, tamoxifen has weak agonist activity in postmenopausal women, thereby reducing bone loss and fracture risk,[12] particularly when compared to aromatase inhibitors.

2.2.2 | Aromatase inhibitors

In women with hormone-responsive breast cancers, therapies which reduce endogenous oestradiol levels have consistently demonstrated superior clinical efficacy. Due to these effects, AIs, as compared to SERMs, are generally considered to be first-line adjuvant therapies in the majority of postmenopausal women presenting with hormone-

responsive breast cancer.[13] However, by further reducing already low endogenous postmenopausal oestradiol levels, AI therapies induce additional bone loss and raise fracture risk in postmenopausal women.

As shown in multiple studies in which postmenopausal women with hormone responsive breast cancer have been treated with an aromatase inhibitor or a SERM, either alone (or in combination as in the ATAC study[14]), AI treatment results in significant BMD declines at both the hip and spine as compared to tamoxifen treatment, and incurs increased fracture risk.[15-17] Notably, AI-induced bone loss occurs with both steroidal and non-steroidal based agents.[18]

Due to the large increases in osteoclast activity that occur with suppression of oestradiol levels, pharmacologic efforts to reduce AI-induced bone loss and fractures have focused almost exclusively on the use of anti-resorptive agents. Multiple well-designed studies have examined the impact of antiresorptive therapies in postmenopausal women with breast cancer receiving AI therapy. Both oral[19-22] and intravenous[23] bisphosphonates have been shown to be effective for reducing AI-associated bone loss and fracture risk. In particular, initiation of bisphosphonate therapy early rather than later (i.e. prior to rather than following on from fracture or decline in BMD) appears to be much more effective for limiting AI-associated skeletal effects.[24] Similar to the bone protective effects of bisphosphonates, treatment with denosumab, a fully humanized monoclonal antibody directed against the osteoclast activating factor RANKL, has been clearly shown to reduce bone loss and fractures in postmenopausal women receiving AI therapy.[25,26] Collectively, these data have led to the establishment of clear guidelines recommending that skeletal health be carefully evaluated in all women with breast cancer at the time of AI therapy initiation, that thresholds for intervention with antiresorptive agents be lowered in AI-treated women relative to women not receiving AI therapy, and that treatment be continued for the duration of AI therapy in women with sufficiently low BMD (*T*-score < −2.0) at time of AI initiation, <−1.5 with one additional risk factor, or in women with two or more risk factors.[27] Recommendations are lacking regarding when one might consider a "holiday" from anti-resorptive therapy in women treated with long-term AI therapy, which in some cases may last up to a decade, reflecting the absence of available data on this important subject.

3 | PROSTATE CANCER

Whereas breast cancer is the most common hormonally-associated cancer in women, prostate cancer is the most common hormone-related cancer in men. As in women with breast cancer, early cancer detection in men with prostate cancer has improved survival length, but has also introduced challenges with respect to treatment-related side effects, including bone loss and increased fracture risk.[28] Prostate cancer is primarily a disease of the elderly (median age at diagnosis in the United States of 66 years),[29] the same population demographic afflicted by normal physiologic age-associated bone loss. In most men, prostate cancer is testosterone dependent at the time of diagnosis, such that approaches aimed at lowering endogenous androgen levels (collectively referred to as androgen deprivation therapy [ADT]) have become the foundation of treatment for most affected men.

Historically, surgical orchiectomy was used to lower circulating androgen levels. The use of both gonadotropin-releasing hormone (GnRH) agonist and antagonist-mediated approaches, however, is now commonplace. Both GnRH agonists and antagonists reduce pituitary release of luteinizing hormone (LH) and lead to reductions in total, bioavailable and free testosterone concentrations, resulting in circulating testosterone levels within the castrate range.[30] Consequently, levels of oestradiol (produced via testosterone aromatization to oestradiol) are also severely reduced. Although testosterone is the dominant male sex steroid, there is good epidemiologic evidence that (as in women) bioavailable oestradiol levels more closely correlate with BMD in men,[2] with abrupt lowering of oestradiol levels as occurs with ADT leading to bone loss,[31] bone microarchitectural deterioration[32] and increased fracture risk.[33] More recently, both abiraterone acetate (which inhibits the key enzyme that catalyses androgen biosynthesis [CYP17]) and enzalutamide (an androgen receptor antagonist) have been developed and approved for the treatment of men with castration-resistant prostate cancer. While both agents have been shown to reduce skeletal-related event incidence, their direct impact on bone mineral density and bone turnover remains unclear.[34,35]

Although the deleterious impact of ADT on the male skeleton is well described, most men initiated on ADT do not receive appropriate therapy to limit these effects.[36] However, the routine incorporation of screening (via DXA imaging) and subsequent treatment algorithms in men with newly diagnosed prostate cancer who are initiated on ADT has been shown to significantly reduce fracture incidence in at-risk men.[37]

Akin to studies in women with breast cancer receiving hormonal therapies, efforts to limit bone loss and fracture risk in men treated with ADT have primarily focused on the use of anti-resorptive agents, with multiple agents as well as denosumab having been studied, albeit in studies which involved fewer subjects than the pivotal trials conducted in women with breast cancer. Among the oral bisphosphonates, both alendronate[38] and risedronate[39] have been shown in randomized, double-blind, placebo-controlled trials in men with prostate cancer initiated on ADT to both increase BMD at the lumbar spine and hip, and to limit the rise in biochemical markers of bone turnover that occurred with placebo treatment. As also seen in women treated with hormonal therapy for breast cancer, a delay in bisphosphonate initiation results in bone loss from baseline, loss which is only partially ameliorated when oral bisphosphonate therapy is subsequently initiated.[40] Only limited data on fracture risk reduction with oral bisphosphonate therapy exists, but is consistent with the anticipated effects of BMD preservation in that bisphosphonate therapy reduces fracture risk.[41]

Similar results to the oral bisphosphonates have also been demonstrated in men treated with intravenous bisphosphonates. Treatment with either pamidronate[42] or zoledronic acid (19758618) maintains or increases BMD at the lumbar spine, femoral neck and total hip relative to placebo, even in men with osteoporosis at time of ADT

initiation.[43] Accordingly, a systematic review and meta-analysis which evaluated relative bisphosphonate efficacy in men treated with ADT for prostate cancer determined that the use of bisphosphonates results in significant reductions in both osteoporosis (relative risk [RR] 0.39; $P < 0.001$) and fracture risk (RR 0.80; $P < 0.01$), with the most significant impact seen in studies of zoledronic acid.[44]

In addition to the clearly defined skeletal benefits of the bisphosphonates, good evidence exists from randomized, double-blind, placebo-controlled trials that denosumab treatment in men receiving ADT for prostate cancer significantly increases BMD as early as one month after therapy initiation at all skeletal sites examined (lumbar spine, hip and distal radius),[45,46] and significantly reduces new vertebral fracture risk.[47] As a result of these findings, denosumab has also been approved for the treatment of men receiving ADT who are deemed to be at high fracture risk.

As noted previously, the aromatization of testosterone to oestradiol is a key feature needed for bone health maintenance in men. With ADT treatment, however, low substrate testosterone levels result in reduced oestradiol levels, ultimately leading to bone loss. This provides a physiologic rationale for treatment with oestradiol or estrogen-like molecules to limit bone loss in men. While the majority of studies have examined the impact of anti-resorptive therapies for limiting the impact of ADT in men with prostate cancer, both oestradiol and SERMs have been studied in randomized, placebo-controlled studies to determine their ability to limit bone loss and fracture risk. Relative to placebo, treatment with the SERM toremifene for 24 months significantly increased BMD at the lumbar spine and hip, reduced biochemical markers of bone turnover, and reduced lumbar spine fractures.[48,49] Notably, however, venous thromboembolic events were increased 2.4-fold in toremifene-treated men, and were most commonly seen in men aged 80 years and older. When only men aged less than 80 years were considered, however, no significant differences in venous thromboembolic events were identified.[50] No SERMs have yet been approved to treat bone loss in men. More recently, a study which examined treatment with low-dose oestradiol in men receiving ADT for prostate cancer demonstrated that topical oestradiol significantly reduced serum levels of the bone resorption marker CTX relative to placebo.[51] Given the short study duration, however, no efforts to assess changes in BMD or fracture risk were undertaken.

4 | GLUCOCORTICOIDS

Overall, glucocorticoid use is the most common iatrogenic cause of bone loss across all clinical indications. Glucocorticoid effects on the skeleton are particularly relevant in cancer therapies, in which glucocorticoids are frequently provided at doses many-fold higher than required for physiologic glucocorticoid replacement, and are often continued for prolonged periods as integral components of standard chemotherapy regimens. For example, prednisone at a higher than physiologic replacement dose is provided to men treated with abiraterone acetate for castration-resistant prostate cancer.

With regard to bone anabolism, glucocorticoids reduce bone formation rates via direct effects on mature osteoblasts. Glucocorticoids also simultaneously increase rates of osteocyte apoptosis. On the bone resorption side of the equation, glucocorticoids induce an initial increase in osteoclast lifespan but ultimately lead to a decrease in osteoclastogenesis.[52] Due to disruption of the normal physiologic coupling that occurs between osteoclasts and osteoblasts, this decrease in osteoclastogenesis also leads to further suppression of osteoblast activity.

In addition to directly affecting bone cells, supraphysiologic glucocorticoid therapy imparts myriad additional effects which negatively impact bone health and fracture risk. These include diminishing intestinal calcium absorption, increasing urinary calcium losses, inducing hypogonadism, and producing proximal muscle weakness.[53] Collectively, each of these non-bone cell effects is detrimental to bone health via the induction of mineral loss from the skeleton and/or via increasing the propensity for falls and fractures. Both anti-resorptive and skeletal anabolic approaches have been shown to be effective and are recommended to prevent and treat glucocorticoid-associated bone loss.[54]

5 | HAEMATOLOGIC MALIGNANCIES

5.1 | Monoclonal gammopathies

Multiple myeloma is a plasma cell malignancy and is the second most common haematologic cancer.[55] Intrinsic to myeloma is the growth of terminally differentiated plasma cells within the bone marrow, where they reside in close proximity to bone. Due to the elaboration of multiple paracrine factors which function to cause simultaneous increases in osteoclast activity and suppression of osteoblast activity, patients with multiple myeloma are frequently found to have osteolytic lesions at the time of diagnosis. In addition, multiple myeloma treatment regimens often incorporate high dose glucocorticoids, which as noted above, are detrimental to skeletal health. Large randomized, placebo-controlled studies have clearly demonstrated that both of the intravenous bisphosphonates pamidronate[56] and zoledronic acid[57] are efficacious for limiting the significant skeletal destruction that characterizes myeloma in most patients. In comparison, treatment with the oral bisphosphonate clodronate has been shown to be comparatively less effective at limiting skeletal-related events in patients receiving anti-myeloma therapies.[58] More recently, a large randomized, double-blind, placebo-controlled study demonstrated that treatment with denosumab was non-inferior to zoledronic acid for the prevention of skeletal-related events in patients undergoing treatment for newly diagnosed multiple myeloma.[59]

All multiple myeloma is preceded by monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant condition with an approximately 1% annual risk for progression to multiple myeloma. MGUS is common and affects approximately 3% of adults aged >50 years, with a prevalence that increases with age. As a pre-malignant condition, MGUS is left untreated, and affected individuals typically

followed by a 'watchful waiting' approach. However, there is good epidemiologic that MGUS is associated with a substantially increased risk for fracture.[60] In turn, this increased fracture risk may in part result from cortical and trabecular bone microarchitectural deterioration leading to reduced biomechanical strength, as has recently been documented in subjects with MGUS.[61,62] Limited data demonstrate that bisphosphonate treatment may be effective to limit bone loss in patients with MGUS, although data on fracture risk in response to anti-resorptive treatment is lacking.[63,64] Finally, in a Phase 3 trial of patients with smouldering myeloma, a condition intermediate between MGUS and multiple myeloma, treatment with zoledronic acid did not reduce the risk for progression to myeloma, although skeletal outcomes were not reported.[65]

5.2 | Paediatric acute lymphoblastic leukaemia (ALL)

Impairment in normal bone mass accrual and an increased prevalence of osteoporotic-type fractures have long been recognized as treatment-associated complications in children with ALL. As recently described by a large consortium which studied 186 children with a median age of 5.3 years over the course of 6 years, the cumulative fracture incidence for vertebral fracture was 32.5%, and 23.0% for non-vertebral fractures.[66] As anticipated based on known skeletal effects, the cumulative glucocorticoid dose was a positive predictor for both types of fractures, with a recent publication demonstrating that bone marrow oedema, evident by imaging in paediatric leukaemia patients receiving glucocorticoids, is predictive of osteonecrosis and eventual bone collapse, particularly in weight-bearing bones.[67]

5.3 | Bone marrow transplantation

Bone marrow transplantation (either autologous or allogeneic) is a used frequently for the treatment of haematologic cancers, and involves bone marrow ablation with chemotherapy and/or radiation during the pre-transplant conditioning period. With improvements in stem cell transplant methodologies, long-term survivorship has increased, but has brought with it attendant problems including increases in skeletal fragility and fracture risk, reflecting multiple factors including conditioning regimens, glucocorticoid use, deficits in nutritional support and often prolonged periods of hypogonadism.[68] In addition to clinical risk factor assessment, the judicious use of anti-resorptive therapies, particularly intravenous bisphosphonates, has been shown to limit bone loss, typically when provided at dosing schedules more intensive than those used for the treatment of osteoporosis.[69] No clinical trials on the use of denosumab in patients undergoing bone marrow transplant have yet been reported.

5.4 | Bortezomib

Bortezomib is the first clinically approved member of the proteasome inhibitor class of chemotherapeutic agents, and has received approval for the treatment of both multiple myeloma and mantle cell lymphoma. In contrast to the other chemotherapeutic agents described, which all result in bone loss and increased fracture risk, bortezomib has been shown in pre-clinical models to have salutary skeletal effects via inhibition of osteoclast differentiation in an ovariectomy-induced model of osteoporosis.[70] In pre-clinical models of multiple myeloma, bortezomib inhibits RANKL-induced osteoclast differentiation and reduces levels of the inhibitor of osteoblast differentiation factor dickkopf-1 (DKK1), thereby leading to increases in osteoblast differentiation and activity. In patients with myeloma, treatment with bortezomib has been shown to increase circulating levels of the bone formation markers bone alkaline phosphatase and pro-collagen type I N-terminal peptide (PINP),[71] and to increase bone volume fraction as well as trabecular thickness in a majority of patients.[72] It is likely that these skeletal effects are not specific to bortezomib, but rather represent a class effect as, at least in preliminary evaluations, increases in biochemical markers of bone formation have also been noted in patients treated with the closely related proteasome inhibitor carfilzomib.[73,74]

5.5 | Imatinib

Imatinib is a tyrosine kinase inhibitor (TKI) approved for the treatment of chronic myelogenous leukaemia (CML), gastrointestinal stromal tumours and other uncommon haematologic malignancies. In a small study of children with CML, imatinib treatment appeared to reduce linear growth.[75] Consistent with these results, a pre-clinical young rodent model showed that continuous imatinib exposure was associated with dose-dependent reductions in long-bone length and BMD, as well as decreased resistance to fracture and lower circulating levels of the bone formation marker osteocalcin.[76] The impact of imatinib treatment in adults is somewhat less clear, but in general available data suggest that over the first 18–24 months of treatment, imatinib may increase early osteoblast differentiation leading to an increase in bone formation.[77] With prolonged imatinib treatment, however, patients frequently develop mild secondary hyperparathyroidism with associated hypophosphataemia.[78] Beyond 24 months of therapy, BMD changes appear to be minimal.[79]

5.6 | Other tyrosine kinase inhibitors

Although best described for imatinib, other tyrosine kinase inhibitors also appear to have effects on bone mineral metabolism, with hypophosphataemia, and in some cases hypocalcaemia, fairly common findings reported in clinical trial results.[80] Long-term skeletal outcomes in patients treated for prolonged periods with these other TKI therapies, however, have yet to be reported.

6 | CONCLUSION

Tremendous progress in the "war on cancer" over the past several decades has led to widespread improvements in survivorship for patients with many types of malignancies, largely the result of a

continuously expanding armamentarium of pharmacologic agents specifically designed to treat malignancy. However, with such improvements in lifespan have frequently come unintended and unanticipated negative consequences, often as a direct result of the cancer therapies themselves. There is now well-established and ever-accumulating evidence, however, that these adverse consequences include heightened risks for both bone loss and fractures. Given these concerns, it is critical for providers and patients alike to recognize that attention to skeletal health is fundamental for maintaining quality of life outcomes. Accordingly, the implementation of comprehensive and well-structured approaches for initial, as well as ongoing, assessments of skeletal health as a cornerstone of care must be considered in these vulnerable patients with cancer.

COMPETING INTERESTS

There are no competing interests to declare.

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