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Skeletal Related Events in Prostate Cancer: Important Therapeutic Considerations

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1. Introduction

In western countries, prostate cancer is the most common non-dermatological malignant disease in men. An estimated 217730 new cases will have been diagnosed in 2010 in the USA (Jemal A et al., 2010) and 382250 cases were diagnosed in 2008 in Europe (Ferlay J et al., 2010), accounting for 28% and 22% of new non-cutaneous cancer diagnoses, respectively.

Bone is one of the most common sites of metastatic disease in patients with cancer, affecting approximately 400,000 patients each year. Nearly 70% of patients with advanced breast or prostate cancer will experience bone lesions; 50% of these patients will develop a secondary skeletal complications which represents a substantial disease and economic burden (Schulman KL & Kohles J, 2007).

The pathologic penetration of bone by tumour tissue can lead to numerous skeletal-related events, such as hypercalcemia, fracture, spinal cord compression, and potentially debilitating bone pain (Berruti A et al., 2002). Often these consequences result in the need for radiological and surgical intervention. Along with these therapies, pharmacological management is required to help reduce symptoms, prevent recurrence and further improve patients' quality of life.

Prostate carcinoma is the most common visceral malignancy and the second leading cause of death from cancer in men (Diamond T et al., 2004). Androgen-deprivation therapy (ADT), either alone (as depot gonadotrophin releasing hormone agonist) or in combination with antiandrogens (such as flutamide, bicalutamide, or cyproterone acetate), is recommended treatment for men with metastatic or locally advanced, non-metastatic prostate carcinoma (Fowler JE et al., 2002). Although it has been demonstrated that this form of therapy significantly reduces tumour growth and improves survival beyond 3 years after completion (Bolla M et al., 1997), there is growing concern regarding the negative effects of ADT on the skeleton. Accelerated bone loss, osteoporosis, and a potential for increased. Fracture rates have been reported in men with prostate carcinoma who are receiving ADT. Because many patients who present with prostate carcinoma are elderly and may have

preexisting osteoporosis, subclinical vitamin D deficiency, or any of a multitude of medical problems, the risk of skeletal deterioration is increased (Elliot ME et al., 2002).

2. Diagnosis of osteoporosis in men

Bone mineral density (BMD) is considered to be the gold standard for diagnosing and assessing the severity of osteoporosis and fracture risk in women. The role of BMD in men is less clear. BMD is measured most commonly by dual-energy X-ray absorptiometry (DXA), but quantitative computed tomography (QCT) of the lumbar spine also is used, particularly in research studies (Faulkner KG et al., 1998).

BMD of the wrist and hip, after adjusting for age, is a strong predictor of fracture risk (Melton L et al., 1998). Although the BMD criteria for diagnosing osteoporosis in men remain controversial (Binkley NC et al., 2002), a definition based on World Health Organization recommendations is accepted currently.

According to definition, osteoporosis exists when the BMD value is > 2.5 standard deviations (SD) below the peak young normal mean reference range (T-score < 2.5). Accurate T-score calculations in individual men can be obtained from bone densitometers using standardized software derived from reference databases for 'healthy' Caucasian men ages 20–40 years. In elderly men, it has been reported that advanced spondyloarthropathy, facet joint disease, and aortic calcification elevate spinal BMD falsely, as assessed by DXA (Zmuda JM et al., 2000). Spinal BMD of the second through fourth lumbar vertebrae should be measured routinely to diagnose osteoporosis. Interpretation of the results often requires the addition of spinal radiographs to improve diagnostic accuracy. QCT of the lumbar spine, using the new three-dimensional multislice scanners, may overcome this problem, but it is not available at many centers; this technique has the ability to accurately define a region of interest unconfounded by extravertebral calcification (Faulkner KG et al., 1998; Weigert JM & Cann CE, 1988). Femoral neck DXA in elderly men, for practical purposes, is used routinely for the diagnosis of osteoporosis, especially if spinal BMD is pseudoelevated. Both spinal BMD and total hip BMD are the preferred sites for monitoring changes in BMD in response to therapies (Kaufman JM et al., 2000; Lenchik L et al., 2002). In a recent study, the relative risk of hip fracture in men was 3.0 (range, 1.7–5.4) for each SD decrease in femoral neck BMD (Delaet C et al., 1998). Longitudinal studies suggest that the rate of lumbar spine bone loss in elderly men is approximately 5–10% per decade, with acceleration after age 75 years. Femoral neck bone loss in normal elderly men is estimated at approximately 0.7% per year (Jones G et al., 2004). A number of factors may increase the bone loss normally associated with aging. These include physical immobility, poor nutrition, reduced calcium dietary intake and intestinal absorption, vitamin D deficiency, increased cytokines, reduced growth factors and osteoblastic activity, and a gradual decline in gonadal androgen production (Kaufman JM et al., 2000). Accelerated bone loss similar to that seen in women undergoing bilateral oophorectomy has been demonstrated in men with hypogonadism who undergo gonadectomy (Daniell HW, 1997) or who receive ADT (Bruder JM & Welch MD, 2002; Yaturu S et al., 2002). In male sex offenders who underwent surgical castration, spinal bone loss occurred at a rate of 4% per year (Stepan JJ et al., 1999). Because these rates of loss are higher compared with the rates of loss observed in otherwise healthy elderly men, the abrupt loss of sex steroids appears to initiate a period of rapid bone loss.

3. Bone health in prostate cancer

In advanced prostate cancer, 65–75% of patients may eventually develop bone metastases. It is also important to note that approximately 10% of men with prostate cancer have bone metastases at initial presentation. Almost all patients who die of prostate cancer have bone involvement (Greenspan SL, 2008).

Men with prostate carcinoma who are treated with ADT are elderly and are at risk for a wide variety of metabolic bone problems. In a recent retrospective study of 125 men with a mean age of 77 years who were treated with ADT, Bruder and Welch reported a 27% prevalence of osteoporosis and a 51% prevalence of osteopenia (lumbar spine or femoral neck BMD T-score, -2.5 to -1.0) (Bruder JM & Welch MD, 2002); furthermore, 44% of the cohort had biochemical evidence of vitamin D insufficiency and secondary hyperparathyroidism.

Osteoporosis has become an increasingly important problem in men's health, accounting for significant morbidity in the aging male population. Patients with prostate cancer treated with ADT are at a high risk of osteoporosis. These patients may have additional morbidity from decreased bone mineralization, such as skeletal fractures. Moreover, a direct association has been noted between fractures and a decreased quality of life and increased mortality (Gilbert SM & Mckiernan JM, 2005).

The prevalence of osteoporosis is lower in men than in women for several physiologic reasons, including a greater accumulation of skeletal mass during growth, greater bone size, absence of midlife menopause, a slower rate of bone loss, and a shorter male life expectancy (Amin S & Felson DT, 2001). The rates of annual bone mass loss in aging men range from 0.5% to 1% compared with 1% to 2% in women (Gilbert SM & Mckiernan JM, 2005; Smith MR, et al., 2001). The prevalence of osteoporosis increases progressively during ADT, reaching almost 50% after 4 years of ADT and more than 80% after 10 years. In contrast, it affects 35.4% of hormone-naïve patients with prostate cancer (Morote J, et al., 2007).

4. Mechanism of metastatic development

In healthy adults, bone physiology is a dynamic, coordinated process controlled by 2 types of cells: osteoclasts and osteoblasts. Through a balanced remodeling process, osteoclasts resorb bone, and osteoblasts build bone at the same site (Coleman RE, 2001; Rosen LS, et al., 2003). This bone remodeling sequence consists of 4 distinct phases: activation, resorption, reversal, and formation.

Bone metastases are often characterized by their radiographic appearance as either osteolytic, osteoblastic, or mixed or mixed. Most patients with breast cancer have predominantly mixed or osteolytic lesions (Coleman RE, 2001; Rosen LS, et al., 2003). In contrast, patients with prostate cancer are often found to have predominantly osteoblastic lesions. However, regardless of appearance, there is significant osteolytic activity. In fact, osteolytic activity in these lesions often is comparable with, if not higher than, that typically seen in breast cancer and multiple myeloma. Such activity has been demonstrated by markedly elevated biochemical markers of bone resorption in the serum and urine of such patients. Only in multiple myeloma do purely lytic bone lesions develop (Coleman RE, 2001; Rosen LS, et al., 2003).

Several mechanisms have been proposed for metastatic spread to the bone. Early animal and human evaluations demonstrated that breast and pelvis tissue drain directly into the veins of the spine, increasing the deposition of metastatic cells into the bone marrow (Coleman

RE, 2006). More recent studies have demonstrated how metastatic lesions develop once cancer cells reside in the marrow. Cellular modulators such as Receptor Activator for Nuclear Factor κ B Ligand (RANKL), parathyroid hormone-related protein (PTHrP), and serine protease urokinase (uPA) disrupt the balance of osteoblast and osteoclast activity that are involved in the formation of metastatic lesions (Mundy GR, 2002). Most bone lesions are classified as osteolytic or osteoblastic, depending on the direction of the bone breakdown/rebuilding imbalance. In osteoblastic lesions (prostate cancer metastases), the production of endothelin-1, transforming growth factor β (TGF- β) and uPA directly increase osteoblast activity and the formation of space-occupying bone lesions. In osteolytic lesions (primarily breast and lung cancer metastases), osteoclast activity is increased through the production of PTHrP, which stimulates nuclear factor κ B (NF- κ B) from stromal cells of bone, leading to increased osteoclast differentiation and activity (Mundy GR, 2002; Saad F, 2008). Newer studies have also shown that RANKL activity in both osteolytic and osteoblastic lesions also may lead to increased tumour proliferation (Uehara H, et al., 2003; Yin JJ, et al., 1999). As osteoclasts break down bone, growth factors are released to stimulate the production of osteoblasts, allowing for bone repair and remodeling. These factors, including TGF- β and platelet derived growth factor have been shown to perpetuate bone metastases in both breast and prostate cancer models (Uehara H, et al., 2003; Yin JJ, et al., 1999).

In metastatic bone disease, RANK Ligand has been implicated in a "vicious cycle" of bone destruction and tumour growth. Some tumours that have metastasized to the bone produce growth factors that can increase expression of RANK Ligand by osteoblasts. This stimulates osteoclast activity and leads to excess bone loss (Coleman RE, 2001; Rosen LS, et al., 2003). Osteoclast-mediated bone resorption leads to the release of growth factors and calcium from the bone matrix, that can in turn stimulate the tumour cell, further contributing to this cycle of bone destruction (Rosen LS, et al., 2003).

5. Bone tissue and effects of hormonal therapy

In life, bone is a rigid yet dynamic organ that is continuously moulded, shaped and repaired. Bone microstructure is patterned to provide maximal strength with minimal mass, as determined by the physiological needs of the organism. How are bone structure and function maintained, and how are changes in bone metabolism induced? Once formed, bone undergoes a process termed remodelling that involves break down (resorption) and build-up (synthesis) of bone; this occurs in micro scale throughout the skeleton. This remodeling cycle is a coupled process; in a normal young adult after completion of normal linear growth, bone resorption and formation are roughly equivalent, resulting in a net bone balance. Bones are composed of 2 main types of tissues: cortical bone and trabecular bone. Cortical bone is 80% to 90% calcified and has mainly mechanical and protective functions. Trabecular bone is only 15% to 25% calcified and constitutes only 20% of the total bone mass, but carries out most of the bone's metabolic function. Bone strength is a function of bone mass and of other parameters including geometry (the diameter of the cortical bone), material properties (the quality of the bone matrix and inorganic crystals) and microstructure (the diameter and interconnectivity of the trabeculae) (Gruber R, et al., 2008). The bone mass of a normal adult is the outcome of a dynamic equilibrium between bone formation (mediated by osteoblasts) and bone resorption (mediated by osteoclasts).

Most adult skeletal diseases are due to excess osteoclastic activity, leading to an imbalance in bone remodelling which favours resorption. Such diseases would include osteoporosis, periodontal disease, rheumatoid arthritis, multiple myeloma and metastatic cancers. For

individuals with osteoporosis, bone fractures represent life-threatening events, and today there are in excess of 70 million people worldwide at risk (Brown JP & Jasse RG, 2002).

Recent breakthroughs in our understanding of osteoclast differentiation and activation have come from the analysis of a family of biologically related tumour necrosis factor (TNF) receptor (TNFR)/TNF-like proteins: osteoprotegerin (OPG), receptor activator of nuclear factor (NF)- κ B (RANK) and RANK ligand (RANKL), which together regulate osteoclast function. Binding of RANKL to RANK on the surfaces of osteoclast precursors will trigger maturation, activation, and prolonged survival of these cells. Thus, RANKL promotes bone resorption. In contrast, OPG is a “decoy receptor” that binds and neutralizes RANKL, thus inhibiting bone resorption (Bayle WJ, et al., 2003). There is interplay between RANKL and OPG.

The ratio of RANKL to OPG is a critical factor determining the balance between bone resorption and bone formation. Vitamin D₃, parathyroid hormone, tumour necrosis factor- α (TNF- α), activated T-cells, and glucocorticoid therapy all increase this ratio, promoting bone resorption. Estrogen deficiency states (including menopause) also produce osteoporosis because normal levels of 17 β -estradiol inhibit RANKL production and stimulate OPG. (Bayle WJ, et al., 2003; Hofbauer LC & Schoppet M, 2004). Testosterone stimulates osteoblasts, inhibits the apoptosis of both osteoblasts and osteoclasts, and is a precursor of estrogen via aromatization; its net effect is to stimulate bone formation. Estrogens are essential in bone formation and resorption in men, and low levels are associated with loss of BMD and fracture risk. (Boonen S, et al., 2008).

In osteoporosis, resorption usually exceeds formation with the net effect of bone loss, decreased strength, and an increased risk of fracture. The hypogonadal state resulting from cancer therapy enhances osteoclastic bone resorption, promoting bone loss, which along with other important clinical factors such as age, prior fragility fracture, and family history lead to increasing fracture risk (Gleason D, et al., 2003; Major PP & Cook R, 2002). In males with hypogonadism (whether induced by orchiectomy, ADT, hyperparathyroidism, or other causes), both testosterone and estrogen levels fall, shifting the balance of bone turnover toward resorption (Higano CS, 2008; Perez et al., 2006). It has been hypothesized that several malignancies including prostate and breast cancer and multiple myeloma also promote bone resorption by expressing or stimulating RANKL (Boyle WJ, 2003).

The use of androgen deprivation therapy (ADT) in prostate cancer patients induces hypogonadism causing significant bone loss often leading to osteoporosis and an increased risk of fracture that may be compounded by the presence of bone metastases. Bone metastases disrupt the normal bone remodeling process by increasing bone resorption, which weakens the bone matrix and increases the risk of other bone complications, such as spinal cord compression, impaired mobility and bone pain (Berruti A, et al., 2001). Bone mineral density (BMD) is reduced by 0.6–5.3% annually in patients with locally advanced disease and 2.3–6.6% in patients with metastatic disease receiving ADT, exceeding by 5 to 10 fold the normal bone loss rates of similarly aged otherwise healthy men and prostate cancer patients not receiving ADT (Casey R, et al., 2006; Michaelson MD, et al., 2007; Smith MR, et al., 2008). Consequently, patients receiving ADT are 7–45% more likely to experience a fracture than patients not receiving ADT (Shahinian VB, et al., 2005; Smith MR, et al., 2006). Bisphosphonates have been shown to prevent bone loss and related complications in patients with locally advanced and metastatic prostate cancer and should be considered as part of cancer treatment when ADT is initiated in these patients. Androgen deprivation therapy is increasingly being prescribed both for men with locally advanced or high-risk non-

metastatic prostate cancer and for those with recurrent disease (Meng MW, et al., 2002; Sharifi N, et al., 2005). With this increased exposure to ADT, clinicians have seen the emergence of longer-term treatment complications, including osteoporosis and osteopenia. Although osteoporosis is generally less frequent in men, it is increasingly recognized as a source of substantial morbidity and even mortality in the aging male. Men suffer one third of all hip fractures. Osteoporotic vertebral fractures have a radiological prevalence of up to 50% in both sexes; they often cause chronic pain, and even clinically silent fractures are associated with increased risks of future fracture (both vertebral and hip), kyphosis, restricted lung function, impaired activities of daily living and even increased mortality (Mavrokokki A, et al., 2007). A study of Canadian prostate cancer patients who were orchiectomized found that their 5-year risks of vertebral and hip fractures were 2.2 fold higher than those of patients who had not been orchiectomized ($p < 0.001$ for both) (Body JJ, 2003).

Fractures also independently predict diminished survival in prostate cancer patients on ADT. In one retrospective study, a history of fracture since the diagnosis of prostate cancer decreased median overall survival from 160 months to 121 months ($p = 0.04$) (Oefelein MG, 2002).

6. Non-invasive markers of bone turnover in normal men and in men with prostate carcinoma treated with androgen deprivation therapy

The slow dynamics of bone turnover and the infrequency with which bone density is monitored following castration in prostate cancer cases justify the recent increasing interest in studying the effects of ADT and the pathophysiology of bone metastasis.

Bone loss in elderly men occurs predominantly as a result of increased bone turnover. On bone histomorphometry, trabecular plate thinning and endocortical bone resorption is evident (Clarke BL, 1996). Non-invasive serologic and urinary markers of bone turnover now can be quantitated accurately. Markers of bone formation, such as bone-specific serum alkaline phosphatase, osteocalcin, procollagen type I propeptides and bone glaprotein, are usually normal in elderly men; whereas markers of bone resorption, such as urinary deoxypyridinoline excretion rates and the NTx and CTx telopeptides of Type I collagen and pyridinolines, often are found to be elevated (Khosla S, 1998).

7. Patients at high risk of bone disease. Who should be screened?

Gold-standard therapeutic care for relapsed hormone-sensitive prostate cancer (HSPC) patients demands chemical or surgical hormonal blockade over the course of the therapeutic strategy. With the advent of prostate-specific antigen (PSA), early detection of HSPC recurrence and early hormonal blockade has become possible. In turn, this may lead to osteoporosis and bone fragility (Smith MR, 2003). Pathological fractures related to osteoporosis are very expensive (Groot MT, et al., 2003) and highly correlated with decreased survival with mortality in the first year as high as 70% (Berruti A, et al., 2000).

There are 4 robust, independent risk factors for osteoporotic fracture described: low bone mineral density (BMD), a prior fragility fracture, age ≥ 65 and a family history of osteoporosis (Brown JP, & Josse RG, 2002). There are also other risk factors for osteoporosis, including lifestyle and dietary factors, such as smoking, excessive intake of alcohol or caffeine, inadequate dietary calcium intake, weight < 57 kg or loss of $> 10\%$ of weight at age 25 and diseases and treatments associated with bone loss (Brown JP, & Josse RG, 2002; Greenspan SL, 2008).

Prostate cancer itself is associated with osteoporosis, even among ADT-naïve patients without metastatic disease. In a cross-sectional study, 45.2% of such patients had osteopenia and 35.4% had osteoporosis even before starting ADT. Systematic retrospective reviews have also shown the association between ADT and increased fracture risk (Saad F, et al., 2008; Brufsky AM, 2008).

Because age and hypogonadism are both considered major risk factors for osteoporosis, all prostate cancer patients beginning ADT should be screened with DXA scans at baseline; anyone aged ≥ 65 and anyone with kyphosis, back pain, substantial height loss, or other symptoms suggesting vertebral fractures should also be screened with thoracic and lumbar spine x-rays.

8. Incidence and presentation of skeletal-related events

The progression of metastatic bone disease in patients with prostate cancer can lead to debilitating skeletal-related events (SREs) (Oofelein MG, et al., 2002). About 70–80% of patients with metastatic prostate cancer present with or develop bone metastasis (Polascik TJ, 2008), and are at increased risk for skeletal-related events (SREs), which include pathological fractures, spinal cord compression (figure 4), and severe pain requiring radiotherapy or surgery for bone lesions. These SREs result in significant complications that reduce quality of life (Botteman MF, et al., 2010).



Fig. 4. Total disruption of the 9th dorsal vertebral body due to a metastatic prostate carcinoma, with spinal cord compression.

Skeletal-related events (SRE) include any secondary complication from the presence of bone metastases and can occur in both osteolytic and osteoblastic lesions. Pain is the most common symptom of bone disease and is thought to be due to increased sensitization of nociceptors, tumor infiltration of nerve channels, and local tissue acidification during the bone resorption process. Often the pain is described as dull, aching, or constant, with increasing intensity with weight-bearing activities. In many patients, this is localized to the area of infiltration (most often the thoracic spine), but may be referred or radicular if there is compression of the nerve channels. In nearly one-third of patients with bone metastasis, pain is caused by pathologic fracture. Similar to osteoporosis, this is often caused by the lytic breakdown of bone, often in the ribs, spine, and long bones. Pain is the most common symptom of fracture, although some patients may develop kyphosis from compression of the spine. In approximately 6% of patients, fracture may lead to the development of neurologic symptoms (Boyle WJ, et al., 2003).

Another cause of neurologic symptoms in patients with metastatic bone disease is malignant spinal cord compression. This medical emergency often is caused by direct compression of the spinal canal by osteoblastic tumor formation and edema or necrosis of the spinal cord from alteration of arterial and venous blood flow. Patients often present with severe back pain, weakness, paralysis, paresthesias and decrease in bowel or bladder control (Sathiakumar N, et al., 2011). At presentation, up to 68% of patients are unable to walk. Prompt management of this complication is necessary to decrease the progression of irreversible neurologic damage. Prevention and early treatment is paramount because the ability to regain ambulation after treatment is a strong predictor of overall survival (Sathiakumar N, et al., 2011; Aljumaily R, & Mathew P, 2011).

Hypercalcemia, defined as serum calcium >10.5 mg/dl, is another common presentation of skeletal metastasis. While the release of calcium into the blood from bone breakdown is the most common mechanism in patients with bone metastasis, hypercalcemia may also occur due to parathyroid hormone imbalances in patients without skeletal lesions. Hypercalcemia is a multifactorial complication of malignancy. Radiation therapy, surgical stabilization, and/or decompression often are necessary in patients with bone metastasis, particularly when the spinal column is involved. Pharmacotherapy is the mainstay of hypercalcemia treatment and is almost always used adjunctively with surgery or radiation to manage fractures, malignant spinal cord compression, and the pain of skeletal-related events (Shahinia V, et al., 2005).

Bone pain is the most common type of cancer-related pain, and was deemed to be severe and debilitating in two-thirds of patients. Treating bone pain therefore remains a consideration when managing metastatic bone disease (Coleman RE, 2006).

SRE is a pathology of high cost. A study in 342 patients with prostate cancer and bone metastases revealed that the annual economic effect of medically treating SREs for these patients was \$12,469. Patients most frequently had radiation therapy (89%), followed by pathologic fracture (23%) and bone surgery (12%). Among patients diagnosed as having at least 1 SRE, 78% experienced 1 type of SRE, 17% had 2 types of SREs, and 5% had 3 or more distinct types of SREs. The mean costs associated with SREs in the year after the initial diagnosis of an SRE, adjusted for the censoring of the data, was \$12,469, with the highest costs associated with radiation therapy (\$5930), followed by pathologic fracture (\$3179) and bone surgery (\$2218) (Lage MJ, et al., 2008).

In advanced prostate cancer, 65–75% of patients may eventually develop bone metastases. It is also important to note that approximately 10% of men with prostate cancer have bone

metastases at initial presentation. Almost all patients who die of prostate cancer have bone involvement (Egerdie B et al., 2010).

Men with prostate cancer that develops SRE have a poor prognosis. In a cohort study of 23,087 incident patients with prostate cancer, 569 (almost 3%) presented with bone metastasis at prostate cancer diagnosis, of whom 248 (43.6%) experienced a skeletal related event during follow-up. Of the 22,404 men (97% overall) without bone metastasis at diagnosis 2,578 (11.5%) were diagnosed with bone metastasis and 1,329 (5.9%) also experienced a skeletal related event during follow-up. One and 5-year survival was 87% and 56% in patients with prostate cancer without bone metastasis, 47% and 3% in those with bone metastasis, and 40% and less than 1% in those with bone metastasis and skeletal related events, respectively. Compared with men with prostate cancer without bone metastasis the adjusted 1-year mortality rate ratio was 4.7 (95% CI 4.3-5.2) in those with bone metastasis and no skeletal related events, and 6.6 (95% CI 5.9-7.5) in those with bone metastasis and a skeletal related event. The result of this study brings the conclusion, that bone metastasis and skeletal related events predict poor prognosis in men with prostate cancer (Norgaard M, et al., 2010).

9. Treatment for prostate cancer induced bone loss: Current options and new horizons

Prostate cancer is the most frequently diagnosed non-cutaneous cancer and the second leading cause of cancer deaths among men in the United States. The 5-year relative survival among men aged 65 years or older is 99.8% for all tumour stage groups combined but is considerably lower (5%) among men with distant metastatic disease at diagnosis (Aapro M, et al., 2008).

Advances in cancer therapies have extended patients' lives and improved patients' outcomes. Because cancer patients are living longer, they may be at an increased risk of metastatic bone pain and untreated bone metastases. As anticancer therapies have extended overall survival, the likelihood that a patient with advanced cancer will live long enough to experience an SRE increases.

Approximately 70% of patients with advanced prostate cancer develop skeletal metastases, which are often associated with significant morbidity and mortality (Coleman RE, 2001). In addition to the skeletal effects of cancer itself, bone loss resulting from treatment is an emerging problem. The causes of cancer treatment-induced bone loss (CTIBL) include the hypogonadal state induced by cancer therapies (testosterone deficiency secondary to androgen deprivation from gonadotrophin-releasing hormone [GnRH] agonists and surgical castration in prostate cancer). This hormone depletion promotes osteoporosis and increases the risk of fracture. This type of patients with malignant bone disease are at risk for skeletal-related events, including pathological fracture, metastases requiring surgery or radiation therapy to bone, and spinal cord compromise. They may experience fragility fractures either because of co-morbid conditions or because of toxicities of their cancer therapy, thus the prevalence of osteoporosis increases during ADT, preventive measures are recommended.

Fracture remains the most significant clinical end point related to CTIBL resulting from ADT. Moreover, fractures are an independent adverse predictor of survival in patients with prostate cancer (Oefelein MG, et al., 2002). No prospective data are yet available regarding the impact of ADT on fracture rates; nevertheless, several retrospective analyses provide

significant evidence for increased fracture risk. An analysis of 15,716 men with fractures and 47,149 matched controls in a nationwide, population-based, case-control study found that prostate cancer is associated with increased risk of fracture (odds ratio [OR] 1.8; 95% CI, 1.6 to 2.1), with an even higher increased risk of hip fracture (OR 3.7; 95% CI, 3.1 to 4.4). However, there was no increased risk of vertebral fractures, which are frequently underreported in the absence of sequential spine x-rays. When adjusted for prostate cancer, age, and previous fracture, an increased fracture risk was seen for both GnRH agonists, with or without non-steroidal anti-androgens (OR 1.7; 95% CI, 1.2 to 2.5; P .01), and orchiectomy (OR 1.7; 95% CI, 1.2 to 2.4; P .01).

Because survival in men with non-metastatic prostate cancer treated with hormone therapy is long (median survival time is 7 years), (Antonarakis ES, et al., 2007) long-term issues of bone health are of particular significance. Moreover, men with untreated disease tend to have lower BMD than their peers and, therefore, are at higher risk for fracture before beginning ADT (Smith MR, et al., 2001).

The identification of the incidence of CTIBL among patients with prostate cancer raises issues for clinicians, including the identification of those at increased fracture risk and appropriate preventative strategies. These questions are of concern not only for the specialist, but also for general practitioners who will frequently encounter these patients. Pharmacotherapy is key to the prevention and treatment of skeletal-related events. Successful treatment of the tumour is the best method of preventing skeletal-related events. Current measures in the treatment of CTIBL and others are cited below.

9.1 Lifestyle measures, calcium and vitamin D supplementation

Lifestyle modifications to address osteoporosis include exercise, smoking cessation and moderating alcohol and caffeine intake. In addition, men over 50 should have a total of 1500 mg daily of calcium and 800 IU daily of vitamin D (D3 being preferable to D2) (Brown JP, et al., 2002). However, the Osteoporotic Society of Canada guidelines state that while adequate calcium and vitamin D (whether dietary or supplemented) are essential adjuncts to prevent and treat osteoporosis, they are insufficient by themselves as treatments.

9.2 Bisphosphonates

Bisphosphonates (BPs) are often used for patients with bone metastases to prevent pathologic fractures, reduce bone pain or control hypercalcemia, but they are not specifically indicated for the prevention and treatment of cancer treatment induced bone loss. Numerous randomized controlled trials have explored the effects of BPs on BMD in the setting of ADT for non-metastatic prostate cancer (Greenspan SL, et al., 2007; Greenspan SL, et al., 2008), but to date none have had sufficient power to demonstrate a reduction in fractures. These trials demonstrate clearly that BPs are effective in reducing BMD loss associated with ADT for at least 1 year (Saad F, et al., 2008).

Since the mid-1990s, bisphosphonates have become a mainstay of the management of metastatic bone disease from breast, lung, and prostate cancer. They are the primary treatment of hypercalcemia, widely recommended to reduce the pain associated with metastatic disease and are the only class of agents approved to prevent the development of skeletal-related events.

Several placebo-controlled trials have demonstrated the (Coleman RE, 2004) benefit of using these agents to prevent skeletal-related events in patients with known bone metastasis.

Bisphosphonates have some limitations. First, long-term efficacy data are sparse. Oral BPs are poorly absorbed, must be taken on an empty stomach and often produce gastrointestinal side effects. Thus, long-term adherence to oral BPs tends to be poor; studies of 1-year adherence to BPs in postmenopausal women have found adherence rates under 60% even with once monthly treatments (Boonen S, et al., 2008). Due to lack of compliance, intravenous BPs are preferred to oral BPs; influenza-like acute phase reactions on initial administration are common but mild, while acute tubular necrosis is rare but serious.

9.2.1 Effect of bisphosphonates on preventing or treating bone complications

The use of bisphosphonates is an emerging therapy for preventing and treating osteoporosis and fractures in the management of recurrent and advanced prostate cancer disease. Moreover, these substances can act as pain relief agents (Verreuther R, 1993; Rodrigues P, et al., 2004). Bisphosphonates, synthetic analogs of the endogenous pyrophosphate molecule, inhibit osteoclast-mediated bone destruction by a decrease bone resorption in patients receiving ADT and/or with metastatic disease (Smith MR, 2003; Ryan CW, et al., 2006; Lipton A, 2004). These drugs selectively adsorb to mineral surfaces on bone that are surrounded by osteoclasts. The bisphosphonates are then released from the bone surface, where they are internalized by and disrupt the bone-resorbing action of osteoclasts (Lipton A, 2004). At least two types of bisphosphonates exist: non-nitro-gen-containing bisphosphonates (clodronate, etidronate) and the more potent nitrogen-containing bisphosphonates (alendronate, ibandronate, pamidronate, risedronate, zoledronic acid) (Lipton A, 2004). Both types of bisphosphonates have been evaluated in prostate cancer patients at risk of bone complications. Pamidronate has been shown to maintain BMD during ADT, whereas alendronate and zoledronic acid have been shown to increase BMD during ADT (Casey R, et al., 2006; Greenspan SL, et al., 2007). Zoledronic acid has also been shown to prevent metastatic disease induced bone complications (for example, fractures, spinal cord compression) in patients with hormone-refractory disease (Saad F, et al., 2002; Saad F, et al., 2004). At this time, no bisphosphonate is indicated for the prevention or treatment of ADT-induced bone loss; however, alendronate is indicated for treatment of men with osteoporosis (Higano CS, 2004). A randomized controlled trial demonstrated that a single infusion of zoledronic acid suppressed bone turnover for at least 12 months and increased BMD of the hip and spine in men receiving a GnRH agonist for non-metastatic prostate cancer. Compared with placebo, zoledronic acid increased BMD of the lumbar spine and hip by 7.1% and 2.6%, respectively (Berenson JR, 2005).

Bisphosphonates have been shown to decrease the risk of skeletal complications by approximately one third (Body JJ, 2003). In addition, bisphosphonates are clinically important for the treatment of hypercalcemia of malignancy and can reduce cancer induced bone pain. The two bisphosphonates approved by the FDA for use in patients with cancer involving bone are pamidronate and zoledronic acid. Clodronate and ibandronate have been licensed for use in malignant bone disease in other countries. Because of the high frequency of skeletal involvement in advanced cancers, bisphosphonates are routinely prescribed in the practice of medical oncology (Ramaswamy B & Shapiro CL, 2003).

A head-to-head non-inferiority trial of zoledronic acid vs pamidronate demonstrated no significant difference between the treatments. One thousand six hundred forty eight patients with osteolytic multiple myeloma or bone metastasis (osteoblastic or osteolytic) from breast cancer were randomized to receive monthly treatments with zoledronic acid (4 mg) or pamidronate (90 mg). The development of skeletal-related events was equivalent in the

zoledronic acid and pamidronate groups (47% vs 51%, respectively), although fewer patients on zoledronic acid required radiotherapy (19% vs 24%; $p = 0.037$). Likewise, the time to skeletal-related events was similar at 376 days in the zoledronic acid group vs 356 days in patients treated with pamidronate ($p = 0.151$), although in a subgroup analysis of breast cancer patients on hormonal therapy, zoledronic acid appeared slightly more efficacious ($p = 0.047$). From this trial it was determined that there was equal benefit for patients using pamidronate or zoledronic acid (Rosen LS, 2003). When treating patients with skeletal lesions from cancer, current oncology practice in the United States typically uses either pamidronate, 90 mg, infused over at least 2 h every 3–4 wk, or zoledronic acid, 4 mg, infused over at least 15 min every 3–4 wk (Hillner BE, et al., 2003; Coleman RE, 2004). With the FDA approval of zoledronic acid in 2001, this agent has gained popularity in clinical practice because of its efficacy in reducing skeletal-related events and the shorter infusion time. Because of the lifelong risk of skeletal-related events in patients with metastatic bone disease, the clinical practice in the palliative setting has been to continue bisphosphonate therapy indefinitely.

9.2.2 Adverses effects of biphosphonates

Bisphosphonate-associated osteonecrosis of de jaw (ONJ) in patients with malignancy has come to the attention of the medical and dental communities primarily through case reporting, and the number of reported cases has been increasing over the past 3 yr. All bisphosphonates have been associated with cases of ONJ; however, this must be tempered with the acknowledgment of the lack of a consensus definition for ONJ and the unknown incidence of ONJ in the general population. The published literature reviewed by the task force identified <1000 cases (Khosla S, et al., 2007)). There are established guidelines for oral health care before initiating chemotherapy (Bamia A, et al., 2005).

A confirmed case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that did not heal within 8 wk after identification by a health care provider, in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region (Khosla S, et al., 2007).

A suspected case of bisphosphonate-associated ONJ was defined as an area of exposed bone in the maxillofacial region that had been identified by a health care provider and had been present for <8 wk in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region (Khosla S, et al., 2007).

The risk factors for bisphosphonate-associated ONJ are:

Oral bone manipulating surgery, poor fitting dental appliances, intraoral trauma, duration of exposure to bisphosphonate treatment, co-administration of glucocorticoids, comorbid conditions (such as alcohol, tobacco, and malignancies), and pre-existing dental or periodontal disease.

Suggest recommendations for clinical management before initiating bisphosphonate therapy and when the diagnosis of ONJ has been made are as follows.

General recommendations:

- There should be free and complete communication between health care professionals (physicians and dentists) involved in treatment and between health care professionals and patients (Ruggerio SL, et al., 2004). Physicians should encourage patients to inform their dentist that they are taking a bisphosphonate.
- All patients starting or taking bisphosphonates should be informed of the benefits of bisphosphonate treatment. They should also be informed of the risks of

bisphosphonates, including the risk of ONJ, the signs and symptoms of ONJ, and the risk factors for developing ONJ (Ruggerio SL, et al., 2004).

- Patients taking bisphosphonates should be encouraged to maintain good oral hygiene and to have regular dental visits during which they can be instructed in proper dental hygiene and can receive proper dental care. They should be urged to report any oral problems to their dentist and physician.
- Education of physicians and patients about bisphosphonate-associated ONJ is vitally important in all circumstances and particularly in circumstances or locations where the resources to provide dental examinations and treatment are limited.

9.3 Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) often used to treat osteoporosis in women. In a 12-month open-label study enrolling 48 men with nonmetastatic prostate cancer receiving Antiandrogen therapy, the addition of raloxifene 60 mg daily significantly improved bone mass density at the total hip and spine (Smith MR, et al., 2004).

9.4 Bicalutamide

Bicalutamide is a non-steroidal anti-androgen, which increases estradiol levels when given as monotherapy. A 12-month, open-label comparison of leuprolide versus bicalutamide (150 mg daily) in 52 men with non-metastatic prostate cancer showed that bicalutamide increased bone mass density (BMD) at several sites (e.g., lumbar spine BMD +2.5% vs. -2.5%; $p < 0.001$), as well as decreasing fat mass, fatigue, loss of libido and hot flushes compared with leuprolide. Breast tenderness and enlargement were seen more frequently in the bicalutamide group (Smith MR, et al., 2004). Finally, a recent prospective study whose population included 253 prostate cancer patients with osteoporosis found that bicalutamide treatment maintained BMD over 6 years (Wadhwa VK, et al., 2009).

9.5 Corticosteroids

Corticosteroids are used most commonly in patients that develop spinal cord compression, but may also be used in those with diffuse pain unresolved with bisphosphonate and analgesic use. As potent anti-inflammatory agents, they improve neurologic symptoms and pain through the reduction of vasogenic edema around the spinal cord. Dexamethasone is often the preferred agent due to its increased potency and central nervous system penetration (Kilmo P, et al., 2004).

Often a loading dose of 10 to 100 mg is administered, followed by a 16- to 96-mg/day maintenance dose, although controversy exists over which dose is more efficacious. High doses have been recommended (100 mg loading dose followed by 24 mg every 6 hours \times 3 days) to quickly restore ambulation, although may increase the incidence of serious adverse effects (Kilmo P, et al., 2004; Cole J, et al., 2008; Heimdal K, et al., 1992). Systematic reviews of the literature found a shortage of quality data, but came to the following conclusions: "There is good evidence to support the use of high-dose dexamethasone (96 mg/d)" in non-ambulatory patients, "but inconclusive evidence for the use of moderate-dose steroids (16 mg/d) in conjunction with radiotherapy for the treatment of MSCC (Loblaw D, et al., 1998). They also state that there is fair evidence for not using steroids in non-paretic patients, although this is not common practice (Loblaw D, et al., 1998; Coleman RE, 2004).

Adverse effects of steroids include insomnia, increased appetite, edema, hyperglycemia, leukocytosis, increased risk of infection, and gastrointestinal bleeding. Patients receiving high doses are at increased risk of these effects and should receive close monitoring; ulcer prophylaxis should be considered. Since adrenal suppression is likely when doses are continued beyond 5 to 7 days, doses should be tapered when discontinuing therapy with these agents (Loblaw D, et al., 1998; Coleman RE, 2004).

9.6 Analgesics

Both opioid and non-opioid analgesics are recommended for the symptomatic treatment of pain. Clinical trials show that bisphosphonate therapy improves pain control and allows most patients to use lower opioid doses; however, bisphosphonates should be viewed as adjunctive for pain control because nearly all patients will require analgesics.

In patients with mild pain, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are acceptable agents to use. Acetaminophen is preferred in patients with thrombocytopenia, renal dysfunction, those receiving nephrotoxic agents, or at risk for gastrointestinal bleeds. In patients with liver dysfunction, NSAIDs are preferred for mild pain (Wadhwa VK, et al., 2008).

Since most patients experience moderate to severe pain, opioid analgesics often are used. Patients naïve to opioid therapy should begin with low doses of immediate release agents (typically 5-15 mg orally morphine or 2-4 mg intravenous morphine) and reassessed every 1 to 2 hours for effect. After 24 hours of pain control on a short-acting regimen, patients should be converted to a long-acting agent such as sustained release morphine, oxycodone, fentanyl, or methadone for basal control. Patients who are opioid tolerant should begin with higher doses of short-acting agents; if they are on a long-acting product, this should be continued, increasing the dose as needed to account for short-acting opioid use. A similar approach should be taken in patients initiating opioid therapy as an outpatient, with a short-acting opioid available every 3 to 4 hours and close follow-up. A bowel regimen with a stimulant plus stool softener should be initiated to prevent constipation from opioid use. The National Comprehensive Cancer Network (NCCN) provides a useful guideline for pain management in cancer patients (Coleman RE, 2004).

Adjunct agents such as anticonvulsants (gabapentin, lamotrigine, topiramate), tricyclic antidepressants (amitriptyline, imipramine, desipramine, nortriptyline), venlafaxine, duloxetine, or topical analgesics (lidocaine or capsaicin) may also help to reduce neuropathic pain caused by nerve compression (Cole J, et al., 2008).

9.7 Upcoming agents: Toremifene citrate and denosumab

The effects on BMD of toremifene citrate, a new SERM, were tested in a 6-month, placebo-controlled dose-finding study with 46 men with prostate cancer receiving ADT. An oral dose of 60 mg daily significantly improved BMD and decreased hot flushes (Steiner MS, et al., 2004). A 2-year, double blind, placebo-controlled phase-III multicentre study of oral toremifene 80 mg has been completed in 1389 ADT patients with advanced prostate cancer; this compound reduced new morphometric vertebral fractures (the primary endpoint) by 53% ($p = 0.034$). Bone mineral density at lumbar spine, hip, and femur was also increased significantly ($p < 0.0001$), and lipid profiles were improved compared with placebo (Smith MR, et al., 2004; Schwarz EM & Ritchlin CT, 2006).

In advanced prostate cancer, metastasis is sadly inevitable. Although bone metastases from prostate cancer have a predominantly osteoblastic appearance, histological findings

(Roudier MP, et al., 2008) and analysis of bone turnover markers (Brown JE, et al., 2005; Demers LM, 2003), support the view that excess osteoclastic activity induces bone destruction in these metastases. The Receptor Activator of NF- κ B Ligand (RANKL) is the main driver of osteoclast formation, function, and survival (Boyle WJ, et al., 2003). Lymphocytes infiltrate the tumour, causing upregulation of nuclear factor-Kappa B (RANK) ligand (RANKL) and lymphotoxin (Luo et al., 2007). Denosumab is a fully human monoclonal antibody that specifically targets RANKL and is delivered by subcutaneous injection twice a year (Schwarz EM & Ritchlin CT, 2006). This therapy was found to be very effective in reducing fractures and was well-tolerated in the clinical settings of osteoporotic postmenopausal women (McClung MR, et al., 2006; Cummings SR, et al., 2009) and protecting BMD in osteopenic postmenopausal women receiving adjuvant aromatase inhibitors for breast cancer (Ellis GK, et al., 2008). More recently, denosumab (60 mg subcutaneously, every 6 months) was evaluated in a 36-month, phase-III, placebo-controlled randomized clinical trial involving 1468 men with non-metastatic prostate cancer who were receiving ADT.⁴⁸ Compared with placebo, denosumab significantly improved BMD at all sites measured, including lumbar spine (the primary endpoint) by 6.7% ($p < 0.001$), total hip by 4.8% ($p < 0.001$), femoral neck by 3.9% ($p < 0.001$), and distal radius by 5.5% ($p < 0.001$) at 24 months; by the end of the trial (36 months), denosumab dramatically reduced the risk of new vertebral fractures (a secondary endpoint) by 62% ($p = 0.006$), but not overall survival in prostate cancer (Fizzazi et al., 2011).

A recent phase-III study comparing denosumab versus zoledronic acid (Fizazi K, et al., 2011) showed that denosumab was better than the established therapy, zoledronic acid, for the delay or prevention of skeletal-related events in patients with advanced prostate cancer, while there was no difference in overall survival or disease progression.

10. Conclusions

Disease-related skeletal complications are common in men with metastatic prostate cancer. Such events, including fracture, hypercalcemia, spinal cord compression, and severe pain are serious complications of several malignancies. Agents such as bisphosphonates should be used to prevent skeletal-related events; they and other agents such as corticosteroids and analgesics are effective in symptom management of skeletal-related events. Through the use of these agents, along with radiation and surgical therapy, outcomes and quality of life can be improved in patients with metastatic disease. Bone metastasis and skeletal related events predict poor prognosis in men with prostate cancer.

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In this book entitled "Prostate Cancer - Diagnostic and Therapeutic Advances", we highlight many of the significant advances made in our treatment armamentarium of prostate cancer. The book is subdivided into four sections termed: 1) novel diagnostic approaches, 2) surgical treatments options, 3) radiation therapy and its potential sequelae, and 4) medical management and its treatment complications. After reading the present book, readers will be very familiar with the major clinical advances made in our multifaceted treatment approach to prostate cancer over the past decade. This book is a tribute to our pioneering urologists and allied healthcare professionals who have continually pushed forward our traditional therapeutic envelope.

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