

Cancer Treatment-induced Bone Loss

BY ROBERT G. JOSSE, MD, FRCPC

Cancer is the leading cause of death among younger women aged 30 to 54 years, with breast cancer comprising 28% of all cancers in females per year. One in 8 women will develop breast cancer during her lifetime. Of these breast cancers, over two-thirds are estrogen-dependent, ie, they are estrogen receptor (ER) positive. They respond to estrogen with increased growth; thus, estrogen suppression is a major therapeutic target.^{1,2} Prostate cancer is the most frequently diagnosed cancer in American males, accounting for approximately 30% of new cancer cases in 2002. It is the second leading cause of death in males and accounts for 11% of total mortality.³ The American Cancer Society estimates that approximately 230,000 new cases of prostate cancer and 216,000 cases of invasive breast cancer will be diagnosed every year.⁴ Among the most common consequences of breast and prostate cancer is bone involvement. Skeletal complications include fracture and bone metastases. Some 65%-75% of patients with prostate or breast cancers develop skeletal metastases and other skeletal-related events (SRE) that are often used as endpoints in clinical trials, testing preventative and treatment strategies.^{5,6} This issue of *Endocrinology Rounds* examines the pathophysiology of bone metastases in people receiving cancer therapies that cause estrogen and androgen depletion and focuses on treatment options with selective estrogen receptor modulators, aromatase inhibitors, and bisphosphonates in women with breast cancer and bisphosphonates in men with prostate cancer.

Beyond the skeletal effects of cancer, there is the emerging problem of bone loss resulting from cancer treatment. This usually occurs as a consequence of the hypogonadal state induced by cancer therapies, ie, hypogestrogenemia secondary to inhibition of the aromatase enzymes in breast cancer and testosterone deficiency secondary to gonadotropin-releasing hormone agonists (GnRH) and anti-androgens in prostate cancer. This cancer treatment-induced bone loss (CTIBL) – caused by the estrogen and androgen depletion – promotes the development of osteoporosis and increases the risk of fracture.^{4,7}

Pathophysiology of bone metastases and CTIBL^{8,9,10}

Bone is a dynamic tissue undergoing resorption and formation throughout life. This remodeling cycle, which occurs asynchronously in packets of bone (bone multicellular units - BMUs) throughout the skeleton, is a coupled process. In a normal young adult, when linear growth is completed, bone resorption, and formation are roughly equivalent and there is net bone balance. In osteoporosis, resorption usually exceeds formation (the former may be excessive, the latter may be inadequate, or there are various permutations of the two) and the net effect is bone loss, decreased strength, and an increased risk of fracture.

The cellular mechanisms governing osteoclast and osteoblast activity and their interaction are now better understood, although beyond the scope of this article. In brief, cells of the osteoblast lineage – when stimulated by, for example, parathyroid hormone, PGE₂, 1,25-dihydroxy vitamin D, and other activators – release RANK ligand (RANKL), which interacts with the RANK receptor on osteoclast progenitor cells to increase differentiation and proliferation of these cells into active osteoclasts. The osteoblast also produces a decoy receptor, osteoprotegerin (OPG) that dampens or quenches the stimulation by binding to the RANKL thereby, in turn, preventing its binding to RANK on the osteoclast. It is the balance between these processes that helps to maintain skeletal integrity. Estrogen withdrawal in women or androgen withdrawal in men results in osteoclast stimulation due to increased activity of various cytokines, for example, members of the interleukin family and tumour necrosis factor (TNF)- α .

The modern treatment of breast and prostate cancer by decreasing sex steroids enhances osteoclastic bone resorption and promotes bone loss. This increases the risk for fragility fracture and may also enhance the development of bone metastases.

Bone metastases⁹

Once a breast cancer cell becomes embedded in bone, increased resorption is induced, in part, through local secretion of parathyroid hormone-related protein (PTHrP), which



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stimulates osteoclast activity. Also, tumour cells secrete substances that increase RANKL production which, in turn, stimulates osteoclastogenesis. In addition, factors released from resorbing bone attract cancer cells onto the bone surfaces where they become incorporated into the bone and grow to become metastases. This vicious cycle creates a favourable microenvironment for the perpetuation of metastatic tumour growth. It is thought that bisphosphonates help break the cycle by inhibiting resorption and decreasing the production of the factors that attract more cancer cells to the endosteal surface of bone. Moreover, the potent bisphosphonates (eg, zoledronate) may have anti-angiogenic properties that possibly help decrease metastasis growth by preventing development of their critical blood supply.¹¹ In addition, among the many and growing effects of bisphosphonates that have been demonstrated is their ability to inhibit matrix metalloproteinases (MMPs). There is evidence to suggest that prostate cancer cells, which express high levels of MMPs, preferentially metastasize to bone.¹² Preliminary animal studies, specifically a rat model of prostate cancer, reveal that treatment with bisphosphonates can suppress and delay tumour progression in bone.¹³ This has major potential benefit in human disease since bone metastases have been reported in 85%-100% of patients with advanced prostate cancer during the natural course of their disease.¹⁴ In fact, bisphosphonates, specifically zoledronic acid, have been shown to reduce skeletal morbidity rate (number of SRE over time) by over 25%.¹⁵

Although the metastases of prostate cancer are often characterized as osteoblastic they are, in fact, mixed osteoblastic/osteolytic lesions. Metastatic tumour cells release humeral factors such as PTHrP that stimulate osteoclastic recruitment and differentiation. Moreover, these prostate cancer cells concomitantly produce soluble paracrine factors (TGF- α , IGF, BMP [bone morphogenetic protein]) that cause osteoblast activation. A similar vicious cycle, as described with breast cancer, is perpetuated as osteoclastic activity releases growth factors (TGF- α) from bone that stimulate further tumour cell growth. It is the interplay and interaction of the different growth factors on cell populations in the bone microenvironment that results in the pattern of metastatic disease that often favours osteoblastic lesions.¹⁵

CTIBL with breast cancer

Estradiol, the most potent endogenous estrogen, is synthesized from androgens by the cytochrome P450 enzyme complex called aromatase. The highest enzyme levels are present in the ovaries of premenopausal women, in the placenta, and in the peripheral adipose tissues of postmenopausal women and men. To reduce the growth-stimulating effects of estrogen on breast cancer, two principal strategies have evolved: blocking estrogen from binding to its receptor and decreasing estrogen production.

Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene accomplish the former and the aromatase inhibitors (AIs), the latter. There are 2 types of AIs:

- nonsteroidal competitive inhibitors (eg, anastrozole and letrozole)
- a steroidal, non-competitive irreversible inhibitor, exemestane.¹

Tamoxifen has long been regarded as the standard of care for adjuvant endocrine treatment of early breast

cancer.¹⁶ Five years of adjuvant tamoxifen therapy compared to placebo provides a 10-year benefit in mortality in early estrogen receptor (ER) positive breast cancer for both node positive (32% versus 45.5%) and node negative (12.2% versus 17.5%) patients.¹⁷ Along with this survival advantage, there is also some protective effect on bones and lipids. However, there are also negative effects, eg, increased risk of endometrial cancer and thromboembolic disease. Moreover, prolonged tamoxifen use may be associated with increased tumour resistance.¹⁸ These limitations of long-term use have led to a search for alternative therapies such as clinical use of AIs as adjuvant endocrine therapy in postmenopausal women with hormone-sensitive breast cancer. Recent clinical data have demonstrated that the AIs provide more effective prevention of breast cancer recurrences and a better tolerability profile than tamoxifen in advanced breast cancer.¹⁹ However, their use is associated with bone loss and an increased risk for fragility fractures.

This negative effect is better understood when one appreciates the pivotal role of estrogen in bone metabolism.⁸ Osteoblasts increase OPG and decrease RANKL production when stimulated by estrogen. In addition, several factors (cytokines and growth factors) are increased by estrogen, including IGF-1, TGF- α , and BMP. Moreover, estrogen increases production of inhibitors of osteoclast differentiation and activity (eg, NO [nitric oxide] and TGF- α). The potent stimulators of osteoclast action, IL 1 and 6, are also inhibited. Thus, it can readily be appreciated that a decrease in estrogen will have a detrimental effect on bone. Moreover, CTIBL is typically more rapid and severe than postmenopausal, age-related osteoporosis. (The corollary is that potent bisphosphonates may well be required to halt the process.) In addition, there is pre-clinical evidence supporting a possible relationship between increased bone resorption and the potential for developing bone metastases. Breast cancer is pre-eminent among the cancers that metastasize to bone, with as many as 70% of breast cancer patients having bone metastases at post-mortem.²⁰ This can be associated with significant morbidity and mortality, secondary to pathological fracture, hypercalcemia, pain, and spinal cord compression.⁵

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that predisposes a person to an increased risk of fracture. Bone strength primarily reflects the integration of 2 main features: bone density and bone quality.²¹ Breast cancer is associated with a high vertebral fracture risk (odds ratio [OR] 4.7 from the time of first diagnosis) that can lead to chronic pain, loss of mobility, and loss of functional independence.²²

Available adjuvant endocrine agents differentially affect bone metabolism. Tamoxifen exerts estrogenic actions on the skeleton of postmenopausal women by increasing bone mass,²³ as well as reducing bone turnover and fracture risk.^{24,25} In contrast, the AIs specifically block the conversion of adrenally-secreted androgens to estrogens and, therefore, decrease the bone protective effects of estrogen.

Bone metabolism risk associated with adjuvant endocrine therapy

Anastrozole

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial methodology included reports of adverse events resulting from disturbances in bone metabolism

(eg, fractures).^{26,27} The overall incidence of bone fractures after a median 68-month follow-up was 11.0% for patients randomized to anastrozole alone compared to 7.7% for patients taking tamoxifen alone, (relative risk 1.49; 95% CI, 1.25-1.77, $p < 0.0001$). Although there were more fractures in the anastrozole group, the relative risk of sustaining a bone fracture with anastrozole versus tamoxifen remained stable over time.

The time course of bone fractures observed in the ATAC trial at the 48-month interim analysis demonstrates that fracture risk with anastrozole peaked at 24 months and then appeared to be relatively stable.²⁸ The 6-monthly fracture rates were also stable in both groups and, after an initial increase, fracture rates with anastrozole do not appear to increase over time.

An ATAC, pre-specified, sub-protocol, focusing on bone effects is assessing the 5-year bone mineral density (BMD) of the lumbar spine and total hip in a subset of patients using dual energy X-ray absorptiometry (DXA) densitometry. Preliminary results at a median follow-up of one year indicated that anastrozole may be associated with a modest loss in BMD, while tamoxifen appears to result in a small increase in BMD (estimated percentage change at lumbar spine: -2.59% anastrozole vs. +1.01% tamoxifen).²⁹

While BMD data are of interest, fracture rates are the most clinically relevant endpoint. It is important to note that ATAC was not designed as a bone trial and certain variables were not controlled or measured. For example, of patients enrolled in ATAC, 35% had previous hormone replacement therapy (HRT) and 21% had chemotherapy, both factors with known influence on bone metabolism. The trial included a wide age range (mean 60±9 years) and did not control for known osteoporotic risk factors such as previous fractures or low BMD (Table 1). Fracture incidence was recorded as a secondary, self-reported outcome and there are no data on calcium or vitamin D intake. However, a 7.1% fracture incidence in the anastrozole arm vs. 4.4% in tamoxifen was reported.

Nevertheless, interim data from the anastrozole sequencing trial Austrian Breast Cancer Study Group/Arimidex/Nolvadex Trial 95 (ABCSG/ARNO) also shows significantly more fractures in patients switching to anastrozole (n=27, 2.4%) compared to those who remained on tamoxifen (n=14, 1.2%).³⁰

Conversely, the interim analysis of the Italian Tamoxifen Arimidex (ITA) trial reported no significant difference in bone fractures between the anastrozole (0.9%) and the tamoxifen groups (0.9%, $p = 0.9$).³¹

Letrozole

Interim results on the use of letrozole as initial and second-line therapy after 5 years of tamoxifen are emerging. Recently updated 25.8-month bone metabolism results of the Breast International Group (BIG) 1-98 reveal that initial letrozole therapy was associated with an increased risk of bone fractures compared to treatment with tamoxifen (5.7% vs. 4.0%) ($p = 0.0006$).³²

Results from the MA-17 trial, in which letrozole or placebo was administered after 5 years of tamoxifen therapy show no significant differences in the incidence of bone fracture between the 2 groups (3.6% with letrozole vs. 2.9% with placebo) at a median 2.5 years follow-up. The incidence of self-reported cases of new osteoporosis was significantly higher in patients receiving letrozole compared to placebo (n=209 [8%] letrozole vs. n=155 [6%] placebo, $p = 0.003$).³³

Exemestane

As exemestane irreversibly inhibits aromatase, there has been particular interest in its effects on bone metabolism. Patients in the Intergroup Exemestane Study (IES) trial benefited from the effects of 2-3 years of tamoxifen therapy on bone health before randomization to exemestane or continuation of tamoxifen. At the 30.6-month interim analysis, musculoskeletal side effects were more common with exemestane; however, there was no significant difference in fracture rates (n=72 exemestane [3.1%] vs. n=53 tamoxifen [2.3%], $p = 0.08$).³⁴ Safety data at 37.4 months are similar to the earlier analysis, and continued to show higher incidence of osteoporosis with exemestane (n=175 [8.3%]) compared to tamoxifen (n=145 [6.9%], $p = 0.05$).³⁵

The effects of exemestane on bone were further studied in the IES bone sub-protocol. A preliminary 1-year analysis of 206 patients revealed that the protective effects of tamoxifen were rapidly lost and that differences in BMD appeared within 6 months of stopping tamoxifen treatment and commencing exemestane.³⁶ There was similar bone loss at 12 months for patients who switched from tamoxifen to exemestane, as compared to that seen with other AIs. The absolute difference in bone mineral density was between 2%-3% in the first year of therapy with the AI. Similar changes in BMD are observed in the 'normal' age-matched population; therefore, it is difficult to reliably detect changes of only 2% in the average patient over this interval.

Role of bisphosphonates in adjuvant endocrine therapy

Bisphosphonates are recognized as an effective therapy for osteoporosis. Early studies with clodronate and risendronate, in association with adjuvant chemotherapy, demonstrated that bisphosphonates could provide protection to the normal skeleton and prevent bone loss in women with chemotherapy-induced ovarian failure.^{37,38} The role of potent bisphosphonates in managing the bone loss effects of AIs has been examined in several trials.

The Austrian Breast Cancer Study Group (ABCSG)-12 evaluated the protective effects of zoledronic acid in pre-

Table 1: Osteoporosis risk factors⁵²

Major risk factors	Minor risk factors
Prior fragility fracture (post-40 years old)*	Rheumatoid arthritis
Age (>65 years)*	Low dietary calcium intake
Low bone mineral density (T-score 2.5)*	Smoker
Family history of osteoporotic fracture*	Excessive alcohol intake
Vertebral compression fracture	Excessive caffeine intake (>4 cups/day)
Osteopenia apparent on x-ray film	Weight (<57 kg)
Hypogonadism	Weight loss >10% of weight at age 25
Early menopause (before age 45)	

*Key risk factors

menopausal women who were randomized to treatment with goserelin (LH-RH agonist resulting in reversible ovarian suppression) plus tamoxifen or anastrozole.³⁹ The 401 patients included in the BMD sub-study were evaluated for treatment-induced bone loss (CTIBL) associated with combination endocrine therapy and whether this could be counteracted by zoledronic acid. BMD was measured at baseline, and after 6 months, and 1, and 3 years of endocrine therapy. CTIBL was frequent in pre-menopausal patients receiving combination endocrine treatment and the severity increased with treatment duration, as measured by BMD. CTIBL was more severe when anastrozole was used in combination with goserelin (-16%, t-score -1.6) versus tamoxifen/goserelin (-8%, t-score -1.0). Arms that included treatment with zoledronic acid had stable BMD measurements versus those with endocrine therapy alone (-12% BMD, -1.2 t-score) ($p < 0.0001$). In this study, zoledronic acid appeared to effectively counteract CTIBL and, thus, treatment with bisphosphonates can be considered for patients with CTIBL. Regular BMD measurements are recommended for breast cancer patients receiving combination endocrine treatment.

The Z-FAST (US)/ZO-FAZT (Europe) trial has also been evaluating the protective effects of i.v. zoledronic acid on bone in post-menopausal women receiving adjuvant letrozole with baseline T-scores > 2.0 .⁴⁰ In one treatment arm, zoledronic acid was initiated immediately for bone protection while, in a second arm, treatment was delayed until the first sign of BMD loss. The primary endpoint was the percent change in lumbar spine BMD at 12 months. One-year results from this multicenter, open-label, randomized study suggest that upfront zoledronic acid prevents CTIBL in post-menopausal women with early breast cancer receiving adjuvant letrozole. Lumbar spine BMD was increased by 2.02% from baseline when zoledronic acid was initiated at the start of letrozole treatment compared with a BMD decrease -2.61% with delayed administration, resulting in an overall difference of 4.63% ($p < 0.001$) between the 2 groups. Serum bone markers in a subset of patients ($n = 226$) showed significant suppression over 12 months in favour of “upfront” versus “delayed” zoledronic acid. Thus, upfront zoledronic acid in combination with letrozole as adjuvant therapy for postmenopausal women with early breast cancer may provide a safe and effective treatment option for managing bone loss at 12 months.⁴¹ Further studies and longer follow-up are required to fully define the potential benefits of bisphosphonate therapy in the context of adjuvant AI therapy for early breast cancer.

In summary, AIs may be associated with bone loss in post-menopausal women; however, the extent and duration of excess bone loss versus placebo is uncertain. Current data do not allow rigorous conclusions regarding adverse BMD effects, although there may be an increase in risk of vertebral fractures associated with AIs, possibly more prominent in those with low baseline BMD and increased bone loss risk factors. Clear identification of risk factors for osteoporosis with individual patients should aid treatment decisions when considering starting or switching to an AI.

Table 2: Suggested recommendations for patients starting adjuvant therapy with AIs

- Assess risk factors for osteoporosis and fractures (Table 1 and reference⁵²)
- DXA at baseline
- “Bone hygiene” measures: lifestyle modification that promotes bone health
 - calcium
 - vitamin D
 - smoking cessation
 - modest alcohol intake (<2 units per day)
 - increase exercise activity
- Consider bisphosphonate therapy if T-score ≤ -2.5 or higher, but risk factors for fracture present

Management of bone metabolism risk associated with adjuvant AI therapy

Adjuvant endocrine therapy with an AI may be considered a risk factor for the development of osteopenia/osteoporosis and bone fracture in post-menopausal women due to significant suppression of circulating estrogen levels and resultant enhanced bone resorption.⁴² In the general postmenopausal female population, osteoporosis is a manageable and potentially preventable condition and this should also hold true for those women receiving adjuvant endocrine therapy for early breast cancer. This process begins with a careful baseline evaluation, followed by ongoing monitoring plus/minus appropriate interventions aimed to reduce the risk of future fractures (Table 2).

Prevalent vertebral fractures are strong predictors of risk for future fracture. A study by Lindsay et al showed that 20% of women experienced another fracture within 1 year of their first vertebral fracture, thus justifying a degree of urgency for clinicians in identifying and treating all patients who present with vertebral fractures.⁴³

Summary

Based on the results of the clinical trials, the American Society for Clinical Oncology (ASCO) has recommended that the “optimal” adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an AI as initial therapy or after treatment with tamoxifen.⁴⁴

CTIBL with prostate cancer

Bone disease associated with prostate cancer is multi-factorial. It reflects the effects of treatment for the disease, as outlined below, with androgen deprivation therapy (ADT) causing osteoporosis, as well as the metastatic pattern of the disease where $> 80\%$ of men with metastases have bone involvement. Moreover, compared to men who do not have prostate cancer, those with untreated disease have a high risk of skeletal complications, including low bone mass and fragility fractures.⁴⁵

ADT is commonly used in men with prostate cancer, particularly because emerging data have suggested a progressive survival benefit. Initially, ADT was achieved via orchiectomy with, or without, add-on estrogen therapy. More recently, however, GnRH ago-

nists and anti-androgens have become the favoured ADT approaches. A well-recognized complication is osteoporosis. Among men who have undergone orchiectomy, there is a 2.5-fold increased risk for bone fracture compared to control fracture rates in the community.⁷ Moreover, the cumulative incidence of fractures in patients followed up for 10 years was 65%.⁴⁶ Several prospective studies have examined the rate of bone loss among patients treated with ADT. There appears to be a 3%-5% reduction in BMD per year.⁴⁷ For the first 2 years of ADT, bone loss is progressive (up to 7% loss per year in young men after ADT with orchiectomy) and worse in those with pre-existing risk factors. It may level off in subsequent years although, in some patients, it continues with increasing duration of ADT.⁴⁸ Studies have also examined intermittent ADT and this form of treatment – at least for the duration of the study – has been shown to be associated with lower rates of bone loss because BMD appears to stabilize or even modestly increase during the “off treatment” period.⁴⁹

The mechanisms by which ADT causes osteoporosis are becoming more clear and are probably multi-factorial. Androgens, principally testosterone, mediate osteoblast differentiation and proliferation and also stimulate the production of growth factors such as TGF- α and IGF-1, which may be important for osteoblast multiplication. This accounts, in part, for the larger peak bone mass in men than in women. Androgen deficiency results in reduced vertebral width, reduced femoral neck width, and reduced bone formation at the basic multicellular unit (BMU) level. Estrogen is also important in the male and, indeed, most estrogen is derived from aromatization of androgens. Both androgens and estrogens are required for optimal skeletal growth. Mechanisms of bone accrual are likely due to both anti-resorptive effects and direct anabolic effects and estrogens also appear to be important for maintenance of bone mass in adult men. Thus, both these sex steroids play a role in the prevention of bone loss and both are lost with ADT.^{47,50}

Since the development of osteoporosis is so often symptomless until fractures occur, BMD measurement is necessary to identify the condition; serial measurements can demonstrate the rate of bone loss. DXA is the preferred method for diagnosis and follow-up.

CTIBL produced by ADT can be reversed with bisphosphonate therapy. This class of drugs, stable analogues of inorganic pyrophosphate, is the standard treatment for osteoporosis in women and men. Clinical trials have demonstrated their efficacy in preventing and reversing ADT-induced osteoporosis. The potent nitrogen-containing bisphosphonates (pamidronate, alendronate, risedronate, ibandronate, and zoledronate) inhibit certain enzymes (eg, farnesyl pyrophosphate synthase, FPP) in the mevalonate pathway, downstream from the rate-limiting enzyme HMG-CoA reductase (which is inhibited by the statins). Inhibition of this enzyme (FPP) prevents prenylation of key intracellular signaling molecules. The end result is cessation of osteoclast activity and decreased cell survival with death by apoptosis.

Not all of the potent bisphosphonates have been evaluated in men with prostate cancer, with or without metastases. Among the bisphosphonates that have been

most widely investigated are intravenous pamidronate and the more potent zoledronic acid. Beyond simply reducing bone loss, studies have assessed the efficacy of bisphosphonates in helping to alleviate bone pain, reduce metastatic burden, and generally decrease the number of skeletal-related events (SREs).^{15,45} The results of these studies have often been disappointing or equivocal. However, the most impressive data thus far have been with IV zoledronic acid, which, in a phase III study of patients with advanced prostate cancer and bone metastases, significantly reduced the proportion who experienced skeletal complications and decreased bone pain during the 15-month trial.⁵¹

ADT is being started earlier and used for longer periods of time in men with prostate cancer and there are well-recognized skeletal complications associated with its use, including increased bone loss and risk for fracture. Definitive guidelines for addressing these issues and the related problem of commonly occurring bone metastases have not been proposed. However, many authorities agree that measures to protect skeletal health and prevent SREs are important.^{47,49,50}

Standard recommendations for the treatment of male osteoporosis can be co-opted for men with CTIBL due to ADT. Risk factors for bone loss and fracture should be assessed and BMD measured prior to starting ADT. The rapidity of bone loss can be gauged by repeating the BMD measurement perhaps initially after a year and, possibly, by measuring bone biomarkers at baseline and 3-6 months later.⁴⁷

There is a paucity of data concerning the use of potent oral nitrogen-containing bisphosphonates in prostate cancer. In the presence of metastatic disease to bone, data from studies with IV zoledronic acid suggest that it is the treatment of choice. Additional studies are underway to determine if early use of bisphosphonates can actually prevent bone metastases. Thus, the role of bisphosphonates in CTIBL specifically related to ADT continues to evolve. However, physicians should be aware of the negative effects of standard prostate cancer treatment with ADT and take steps to reduce the risks with currently available treatment.

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