An update on androgen deprivation therapy for prostate cancer

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Abstract

Androgen deprivation therapy (ADT) with gonadal testosterone depletion is the frontline treatment for advanced prostate cancer. Other hormonal interventions have a role in the treatment of prostate cancer. We sought to examine systematically the evidence for hormonal interventions in prostate cancer, risks of ADT, and interventions that mitigate these risks. Search results for therapeutic studies were focused primarily on randomized controlled clinical trials, and the Jadad scale criteria were used to evaluate the quality of these studies. Four trials of the efficacy of intermittent ADT versus continuous ADT were included. One randomized study analysis and six postrandomization analyses were included on the effects of ADT on cardiovascular mortality. Seven randomized controlled trials of pharmacologic interventions were included for the treatment of metabolic effects due to ADT. One randomized trial of GnRH antagonist versus GnRH agonist was included. Six phase I/II clinical trials of secondary hormonal therapies with novel mechanisms of action were included. Randomized studies completed to date indicate that intermittent ADT might be equivalent to continuous ADT. Although adverse effects of ADT include risk factors for cardiovascular disease, effects on cardiovascular mortality are uncertain. Bone loss and increased risk of fracture may be effectively treated with pharmacologic interventions. Benefits of ADT must be balanced with a consideration of the risks.

Introduction

In 2009 alone, there were an estimated 192,280 new cases of prostate cancer and 27,360 estimated deaths due to prostate cancer in the United States (Jemal et al. 2009). Depletion of gonadal testosterone through androgen deprivation therapy (ADT) is the frontline treatment for advanced prostate cancer and may be accomplished by medical or surgical castration. Of the ~2 million men currently diagnosed with prostate cancer in the United States, over one-third have received treatment with ADT (Keating et al. 2006, Saylor & Smith 2010). Those treated comprise the vast majority of the ~27,000 men who die annually from prostate cancer, including men who undergo ADT as primary therapy for localized disease, as an adjunct to radiation therapy for high-risk localized disease, and as treatment for biochemical relapse (prostate-specific antigen (PSA) rise only) after failure of localized therapy, often with uncertain benefits (Sharifi et al. 2005).

Other hormonal interventions for prostate cancer include further depletion of androgens by inhibition of adrenal androgen synthesis, direct inhibition of the androgen receptor (AR), and inhibition of 5α-reductase, which converts testosterone to the more potent dihydrotestosterone (DHT). New and more potent hormonal agents for the treatment of prostate cancer are in phase III clinical trials. The large number of men treated with hormonal therapy for prostate cancer has increased the urgency to understand and effectively treat adverse effects that accompany these therapies. This review is a critical evaluation of new hormonal therapies for prostate cancer, the adverse effects of ADT, treatments that may ameliorate adverse effects, and efficacy of continuous ADT versus intermittent ADT.
Methods

Electronic literature searches of PubMed and Web of Science were conducted for English language articles published between 1966 and February 2010, using the terms prostate cancer, ADT, and hormone treatment. To specifically identify studies on bone loss, cardiovascular endpoints, and intermittent hormonal therapy, the secondary search terms osteopenia, cardiovascular, and intermittent were used. Articles retrieved from clinical studies that were not based on randomized design were excluded. References from selected articles were reviewed manually, and supplemental searches of meeting abstracts from American Society of Clinical Oncology and American Urological Association annual meetings were performed to further identify relevant studies. Articles were further selected for agents with novel mechanisms of action based on randomized study design for clinical trials on ADT and any phase I/II clinical trial for secondary hormonal therapies. To extract these studies, the search terms GnRH antagonist, abiraterone acetate, and MDV3100 were used. The Jadad scale was used to evaluate the quality of randomized controlled clinical trials with emphasis placed on trials with scores ≥2. Finally, other manuscripts were selected to provide appropriate context and a contemporary perspective.

Results

Study inclusion

Emphasis was placed on the highest quality of data. Inclusion of data from trials of pharmacologic agents with novel mechanisms of action of ADT was based on randomized study design for clinical trials on ADT and any phase I/II clinical trial for secondary hormonal therapies. To extract these studies, the search terms GnRH antagonist, abiraterone acetate, and MDV3100 were used. The Jadad scale was used to evaluate the quality of randomized controlled clinical trials with emphasis placed on trials with scores ≥2. Finally, other manuscripts were selected to provide appropriate context and a contemporary perspective.

Table 1 Summary of study search for androgen deprivation therapy for prostate cancer

<table>
<thead>
<tr>
<th>‘Prostate cancer’ and ‘androgen deprivation therapy’ or ‘hormone treatment’</th>
<th>‘GnRH antagonist’, ‘abiraterone acetate’, or ‘MDV3100’</th>
<th>‘Intermittent’</th>
<th>‘Cardiovascular’ or ‘osteopenia’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articles yielded</td>
<td>148</td>
<td>274</td>
<td>704</td>
</tr>
<tr>
<td>Articles reviewed</td>
<td>15</td>
<td>21</td>
<td>31</td>
</tr>
<tr>
<td>Articles selected</td>
<td>One randomized controlled trial and six phase I/II trials</td>
<td>Four trials selected based on randomized design and trial size</td>
<td>Seven randomized controlled trials, one randomized study analysis, and six postrandomization analyses</td>
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ADT is achievable pharmacologically with medical castration or through surgical orchiectomy. Medical castration is generally favored by patients because of the psychological effects and irreversible nature of surgical orchiectomy (McLeod 2003). Bilateral orchiectomy, however, is significantly less expensive than medical castration (Chon et al. 2000).

The common mechanism of the various means of medical castration is suppression of the release of LH from the anterior pituitary. GnRH is a peptide hormone that is synthesized in the hypothalamus and regulates pituitary LH release (Conn & Crowley 1994). The LH response depends on the nature of stimulation by GnRH, and LH is released only in response to pulsatile GnRH secretion (Conn & Crowley 1994). Although administration of estrogens, such as diethylstilbestrol (DES), suppresses pituitary release of LH and the resultant testosterone secretion from the Leydig cells of the testes (Cox & Crawford 1995), treatment with DES is also associated with cardiovascular deaths (Byar 1973) and is therefore no longer used. On the other hand, GnRH agonists are commonly used for medical castration. GnRH agonists are administered s.c. or i.m. for sustained release. Continuous pituitary stimulation by GnRH agonists overcomes endogenous pulsatile GnRH and suppresses LH release, resulting in low serum testosterone (Tolis et al. 1982). Synthetic GnRH agonists include leuprolide, goserelin, and histrelin. A potential disadvantage of GnRH agonists is the initial rise in serum testosterone concentrations when beginning treatment and the potential to induce a consequent stimulation of prostate cancer growth. The effects of the initial testosterone surge can be blocked by AR antagonists (Kuhn et al. 1989). Alternatively, administration of GnRH antagonists, such as degarelix (Doehn et al. 2009), does not induce a testosterone surge. A three-armed, randomized phase III study compared a starting dose of 240 mg degarelix, followed by 80 or 160 mg monthly s.c. doses, with monthly 7.5 mg i.m. doses of leuprolide in 610 previously untreated patients (Klotz et al. 2008). Concomitant treatment with an AR antagonist in the leuprolide arm to prevent an initial testosterone surge and tumor flare was at the discretion...
of the investigator. By day 3, the median testosterone concentration rose from 384 ng/dl (13.1 nmol/l) to 630 ng/dl (21.4 nmol/l) in the leuprolide arm. In contrast, median testosterone concentrations were 24 ng/dl (0.82 nmol/l) and 26 ng/dl (0.88 nmol/l), and 96.1 and 95.5% of patients in the degarelix 240/80 and 240/160 mg arms respectively were below the testosterone castrate threshold of 50 ng/dl (1.7 nmol/l). The PSA decline at day 14 was significantly greater in the degarelix arms, reflecting the faster onset of testosterone decline, although this difference was no longer statistically significant at day 35. On the other hand, the PSA decline was similar between the degarelix arms and men who received leuprolide in addition to AR antagonist. Testosterone suppression to <50 ng/dl (1.7 nmol/l) for all monthly assessments up to 1 year was achieved in 97.2, 98.3, and 96.4% of patients in the degarelix 240/80 mg, degarelix 240/160 mg, and leuprolide arms respectively. Although there were no allergic reactions, in contrast to other trials of GnRH antagonists, treatment in the degarelix arms was associated with a 40% chance of injection-site reactions.

The benefits of ADT in advanced disease include fewer tumor-associated events, such as spinal cord compression, extraskeletal metastases, pathological fracture, and ureteral obstruction (Medical Research Council 1997). ADT adjuvant to radiation therapy increases survival in men with intermediate, high-risk, and locally advanced disease (D’Amico et al. 2004, Bolla et al. 2009, Souhami et al. 2009). Furthermore, there is a survival benefit for men treated with ADT after radical prostatectomy who also have lymph node involvement (Messing et al. 1999).

Other hormonal interventions

Although the majority of prostate tumors initially respond to ADT, metastatic disease almost invariably progresses eventually to castration-resistant prostate cancer (CRPC). Paradoxically, CRPC often remains responsive to other hormonal therapies (Scher & Sawyers 2005, McPhaul 2008, Sharifi 2010) in large part due to the intratumoral regeneration of androgens (Titus et al. 2005, Montgomery et al. 2008). Therefore, after the development of CRPC, patients are often treated with secondary hormonal therapies that further deplete androgen concentrations, or directly bind and inhibit AR (Ryan & Small 2005).

Bicalutamide, nilutamide, and flutamide are nonsteroidal AR antagonists frequently used as secondary hormonal therapy in the United States (Ryan & Small 2005). Of these, bicalutamide binds AR with the highest affinity, has the longest half-life, and is generally the most favored (Gao et al. 2005). Importantly, these nonsteroidal AR antagonists may have AR agonist activity, particularly under certain circumstances associated with CRPC (Kelly & Scher 1993, Figg et al. 1995, Taplin et al. 2003, Chen et al. 2004). Ketoconazole is an antifungal imidazole that inhibits cytochrome P450 enzymes, including 17α-hydroxylase/17,20-lyase (CYP17A1), in the adrenal, which is required for androgen synthesis (De Coster et al. 1996). Secondary hormonal therapy with ketoconazole inhibits the synthesis of adrenal androgens and leads to frequent PSA declines in CRPC (Figg et al. 2005). Treatment with ketoconazole can cause adrenal insufficiency due to declines in other adrenal steroids; patients are therefore supplemented with hydrocortisone (Khosla et al. 1989, Figg et al. 2005). Unfortunately, no survival advantage for CRPC has ever been definitely demonstrated with any of these standard secondary hormonal therapies.

Two investigational hormonal therapies with novel mechanisms of action and promising activity in phase I/II clinical trials are currently in phase III placebo-controlled trials. Compared with ketoconazole, abiraterone acetate is a more specific and potent inhibitor of CYP17A1, with unique clinical activity and adverse effect profiles (Barrie et al. 1994, Haidar et al. 2003). Several phase I/II clinical trials of abiraterone acetate have been completed both in patients who have previously received and in those who have never been treated with ketoconazole and/or chemotherapies (Attard et al. 2008, 2009, Danila et al. 2010, Reid et al. 2010, Ryan et al. 2010). In two trials, serum testosterone was further suppressed from baseline after treatment with abiraterone acetate (median 7 ng/dl at baseline, <1 ng/dl at day 8 (Attard et al. 2008); mean 4 ng/dl at baseline, <1 ng/dl at day 28 (Ryan et al. 2010)). Serum DHEA and DHEA-sulfate (DHEA-S) concentrations also declined in these trials (median DHEA 282.4 ng/dl at baseline, 83.6 ng/dl at day 28 (Attard et al. 2008); median DHEA-S 39 μg/dl at baseline, <15 μg/dl at day 28 (Attard et al. 2008); mean DHEA-S 49 μg/dl at baseline, <15 μg/dl at day 28 (Ryan et al. 2010)). Inhibition of CYP17A1 activity with abiraterone acetate, which blocks the pathway to androgens and other 19-carbon steroids, shunts the steroidogenic pathway to mineralocorticoids. This results in 10- and 40-fold increases in deoxycorticosterone and corticosterone respectively (Attard et al. 2008). As might be predicted, the adverse effect profile includes hypertension, hypokalemia, and edema, which are manageable with the mineralocorticoid receptor antagonist eplerenone (Attard et al. 2008).
These adverse effects may be ameliorated by low-dose glucocorticoids, which suppress ACTH and adrenal steroidogenesis (Attard et al. 2009). Two phase III randomized, placebo-controlled clinical trials are ongoing and will ultimately determine the role of abiraterone acetate for the treatment of CRPC.

MDV3100 is a member of the new class of diarylthiohydantoin AR antagonists (Tran et al. 2009). This drug binds AR with a five- to eight-fold higher affinity than bicalutamide, inhibits AR nuclear translocation, and has reduced agonist activity, distinguishing it from the three nonsteroidal AR antagonists used in current clinical practice. A phase I/II clinical trial of MDV3100 demonstrated PSA declines of >50% in 57% of CRPC patients not previously treated with chemotherapy and 45% of patients who progressed on docetaxel chemotherapy (Tran et al. 2009, Scher et al. 2010). A phase III randomized placebo-controlled trial of MDV3100 is currently underway in patients with CRPC previously treated with chemotherapy, and a second trial will follow for chemotherapy-naive patients.

Continuous ADT versus intermittent ADT

The antitumor effect of intermittent ADT versus continuous ADT has been debated since preclinical studies first suggested that intermittent ADT might allow for multiple cycles and delayed resistance to ADT (Akakura et al. 1993). Furthermore, given the adverse effects of ADT, there may be beneficial effects and potential cost savings in time off therapy with intermittent treatment, particularly if suppressive effects on prostate cancer are equivalent to continuous ADT (Seruga & Tannock 2008).

A randomized trial of intermittent ADT versus continuous ADT in 335 patients with advanced (lymph node-positive or metastatic) prostate cancer demonstrated equivalent survival (51.4 vs 53.8 months, \(P = 0.658\); Miller et al. 2007). Patients in the intermittent arm were off treatment >40% of the time. It is important to note that testosterone recovery after discontinuation of GnRH agonist is often delayed and may depend on treatment duration, age, baseline testosterone, and ethnicity (Gulley et al. 2008). In a trial of intermittent ADT versus continuous ADT for advanced prostate cancer, 193 patients were randomized and, after a mean follow-up of 34 months, no difference in survival was observed (\(P\) value not stated; Langenhuijsen et al. 2008). A larger trial randomized 312 men to continuous ADT and 314 men to intermittent ADT (Calais da Silva et al. 2009). With a median follow-up of 51 months from randomization, there were fewer cancer deaths (84 vs 106), more cardiovascular deaths (52 vs 41), and an equivalent number of total deaths (169 vs 170) in the continuous versus intermittent arms respectively. Median time off ADT was 52 weeks for patients in the intermittent arm (Calais da Silva et al. 2009). It should be noted that the randomization criteria for all of these trials are a PSA decline of 80–90%, or to <4 ng/ml on initial ADT. Furthermore, ADT for all of these trials included treatment with an AR antagonist (Miller et al. 2007, Langenhuijsen et al. 2008, Calais da Silva et al. 2009).

Although current evidence suggests that intermittent ADT may be reasonable for some patients with hormone-sensitive prostate cancer (Seruga & Tannock 2008), there are still questions about patient selection, timing, and methodology of intermittent ADT (Keizman & Carducci 2009). SWOG 9346 is an ongoing randomized trial with an accrual goal of 1512 patients, with a primary objective to determine whether treatment of men with newly diagnosed, hormone-sensitive, metastatic prostate cancer with intermittent ADT and continuous ADT leads to equivalent survival (Hussain et al. 2009). This would be the largest randomized trial of continuous ADT versus intermittent ADT to date and is expected to yield more definitive results.

Adverse effects of ADT

Prostate cancer is generally a disease of older men, many of whom already have other significant comorbidities. In this population, the potential benefits of therapy must be tempered with a consideration of its adverse effects (Table 2). Prospective clinical trials of ADT for men with prostate cancer demonstrate the development of multiple risk factors for cardiovascular disease, including increases in serum cholesterol and triglycerides, insulin resistance, body mass index, and fat body mass, along with decreases in lean body mass (Sharifi et al. 2005, Levine et al. 2010).

### Table 2 Possible adverse effects of androgen deprivation therapy

<table>
<thead>
<tr>
<th>Metabolic effects</th>
<th>Hyperlipidemia, insulin resistance and diabetes, osteoporosis, increased risk of fracture, and anemia</th>
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<tr>
<td>Physical changes</td>
<td>Increased fat mass, decreased muscle mass, loss of body hair, gynecomastia, and hot flashes</td>
</tr>
<tr>
<td>Mental changes</td>
<td>Decreased cognition and emotional changes</td>
</tr>
<tr>
<td>Sexual effects</td>
<td>Decreased libido and erectile dysfunction</td>
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Population-based analyses further suggest that treatment with ADT is associated with an elevated risk for diabetes (Keating et al. 2006, Alibhai et al. 2009).

**Cardiovascular risk**

Randomized study analyses and postrandomization analyses from several clinical trials have examined whether these longitudinal changes in cardiovascular risk factors translate to an increased risk of cardiovascular death. In a pooled analysis of 1372 men in three randomized trials of men receiving radiation for localized prostate cancer and 0 vs 3 vs 6 months, 3 vs 8 months, or 0 vs 6 months of ADT, men 65 years of age or older receiving 6 months of ADT had shorter times to fatal myocardial infarction compared with men not receiving ADT ($P=0.017$; D’Amico et al. 2007). No significant difference was observed in men younger than 65 years of age, or in men 65 years of age or older receiving 6–8 vs 3 months of ADT (D’Amico et al. 2009). In a randomized trial of 206 men receiving 6 months of ADT plus radiation versus radiation alone for localized prostate cancer, 13 deaths from myocardial infarction occurred in each group (D’Amico et al. 2007). In men receiving ADT, however, 11 deaths occurred in men with moderate to severe comorbidities, leading to a loss in overall survival benefit in these men.

On the other hand, other studies from randomized clinical trials do not suggest that ADT confers an increased risk of cardiovascular events. In a randomized trial in 945 men with locally advanced prostate cancer receiving adjuvant ADT with radiation versus radiation and salvage ADT on disease recurrence (RTOG 85-31), the treatment arm was not significantly associated with risk of cardiovascular mortality after censoring for salvage ADT (Efstathiou et al. 2009). In a trial of 1554 men with locally advanced prostate cancer receiving radiation therapy and randomized to 4 vs 30 months of ADT (RTOG 92-02), duration of ADT was not significantly associated with 5-year risk of cardiovascular mortality (4.8 vs 5.9%; $P=0.16$; Efstathiou et al. 2008). The 10-year rate of fatal cardiac events in a randomized trial of short-term neoadjuvant ADT for locally advanced prostate cancer (RTOG 8610) was not significantly different in the arm receiving 2 months of ADT versus no ADT (12.5 vs 9.1%; $P=0.32$; Roach et al. 2008). A randomized trial of radiation plus 6 vs 30 months of ADT in 1113 men with locally advanced prostate cancer (EORTC 22961) showed no difference in the cumulative incidence of fatal cardiac events at 5 years (4.0 vs 3.0%; Bolla et al. 2009). A randomized trial of immediate versus deferred ADT in 985 men with localized prostate cancer not suitable for local treatment demonstrated no increase in cardiovascular mortality in the immediate ADT arm (17.9 vs 19.7%; Studer et al. 2006).

It is presently unclear whether there is a causal relationship between ADT and cardiovascular mortality. The differences in outcome among studies that have examined this issue may be due to study design, characteristics of the study populations, or competing risks. ADT may affect cardiovascular mortality in a subset of these study populations. Alternatively, there may be no causal relationship. It may be prudent to carefully consider the potential risks and benefits before initiating ADT, particularly in patients with coronary artery disease. Patients with cardiac disease who initiate ADT should receive particular attention to secondary preventive interventions (Levine et al. 2010).

**Intervention for hyperlipidemia**

Favorable modification of cardiac risk factors may be beneficial for patients receiving ADT. In an interim analysis of 188 patients receiving ADT in a phase III, randomized, double-blind, placebo-controlled trial of toremifene, a selective estrogen receptor modulator (SERM), patients in the toremifene arm had favorable changes in serum lipid profile at 1 year of treatment (Smith et al. 2008b). In the toremifene arm, mean total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides declined by 8.1, 8.2, and 13.2% respectively, and high-density lipoprotein (HDL) cholesterol increased by 0.5%. In the placebo arm, total cholesterol decreased by 1.0%, LDL cholesterol increased by 0.8%, HDL cholesterol decreased by 4.9%, and triglycerides increased by 6.9%. All comparisons between the placebo and toremifene arms were statistically significant (Smith et al. 2008b). On the other hand, the effects of toremifene on cardiovascular events and mortality are unknown.

**Treatment of ADT adverse effects**

**Bone density and fracture risk**

The conversion of testosterone to estradiol by aromatase in bone is important in maintaining bone density (Guise et al. 2007). Through this mechanism, ADT may lead to a relative estrogen deficiency in bone that may be comparable to the postmenopausal state. Prospective clinical trials have shown that ADT leads to significant decreases in bone mineral density (BMD; Saylor & Smith 2010). Furthermore, a population-based study of 50 000 men suggests that men treated with ADT have an increased fracture risk.
Interventions are therefore required to prevent bone loss and decrease fracture risk in patients receiving ADT.

Bisphosphonates decrease bone loss by inhibiting osteoclast function and bone resorption (Drake et al. 2008). Randomized, placebo-controlled clinical trials of several agents in this class, including pamidronate (Diamond et al. 2001, Smith et al. 2001), alendronate (Greenspan et al. 2007), and zoledronic acid (Smith et al. 2003, Michaelson et al. 2007), have demonstrated that bisphosphonates increase BMD in patients treated with ADT. None of these bisphosphonate studies was large enough to determine the impact on fractures due to ADT (Saylor & Smith 2010).

Given that bone loss from ADT is due to a deficiency of estrogen (Guise et al. 2007), replacement of estrogenic function with SERMs may favorably affect bone density. In a phase III randomized study of placebo versus toremifene (80 mg daily), patients in the toremifene arm had significantly increased BMD in the hip and spine (Smith et al. 2008a). Furthermore, the 2-year incidence of new vertebral fractures was significantly lower in the toremifene arm (2.5%) than in the placebo arm (4.9%; \( P = 0.05 \); Smith et al. 2010). The toremifene arm, however, had more than twice the number of venous thromboembolic events.

The genesis, function, and survival of osteoclasts are critically dependent upon the receptor activator of nuclear factor-\( \kappa \)B ligand (RANKL; Lacey et al. 1998). Denosumab is a human monoclonal antibody against RANKL that inhibits osteoclast activity. A randomized, double-blind, placebo-controlled clinical trial compared denosumab (60 mg s.c.) with placebo, given every 6 months, in 1468 men on ADT for nonmetastatic, hormone-responsive prostate cancer (Smith et al. 2009). At 2 years, patients in the denosumab arm had significantly higher BMD than those in the placebo arm, with 4.8, 3.9, 5.5, and 4.0% increases \( (P < 0.001) \) in total hip, femoral neck, distal third of radius, and whole body BMD values. The relative risk of vertebral fractures for men in the denosumab arm compared to placebo at 1, 2, and 3 years was 0.15, 0.31, and 0.38 \( (P \leq 0.006) \). Over 36 months, fractures at any site developed in 5.2 and 7.2% of patients in the denosumab and placebo groups respectively, although the difference was not statistically significant \( (P = 0.10) \; \text{Smith et al. 2009}. \)

Conclusions
ADT with gonadal depletion of testosterone is widely used as the frontline therapy for advanced prostate cancer, and to treat localized disease in combination with other therapies. Other hormonal therapies that block adrenal steroidogenesis further reduce androgen synthesis, or directly and competitively inhibit the AR. Investigational agents in clinical trials appear to be more potent than those in current clinical use. The role of these investigational agents in earlier stage disease should also be investigated. Intermittent and continuous ADT may be equivalent, and selected patients may be candidates for intermittent therapy with reduced adverse effects. Nevertheless, more definitive results await completion of a larger clinical trial.

Adverse effects of ADT include metabolic changes such as hyperlipidemia, increased fat mass, insulin resistance, and diabetes. Although many of the metabolic effects induced by ADT are risk factors for cardiovascular disease, the effects on cardiovascular risk are uncertain. Pharmacologic intervention may decrease bone loss and reverse increased risk of fracture due to ADT. Patient comorbidities and risk factors for the adverse effects of ADT, such as the history of osteoporosis or prior fractures, as well as the potential value of pharmacologic intervention should be taken into consideration prior to the initiation of ADT.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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