THEMATIC REVIEW

Second-generation hormonotherapy in prostate cancer and bone microenvironment

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Abstract

Prostate cancer (Pca) is the most commonly diagnosed cancer affecting men in France. Before the age of 75 years old, 1 in 8 French men will have Pca. Androgen deprivation therapies (ADT) remain the standard of care. Such therapies induce significant bone loss. The bone-remodelling cycle depends on the androgen synthesis signalling pathways. Furthermore, age-specific hormonal decline plays a key role in the decrease in bone mass. As a result, the older the patients, the more likely they are to have osteoporosis if they are treated with hormone therapy. Their risk of osteoporotic fracture has an impact on their quality of life and their capacity of independent living. In recent years, newer hormone therapies (acetate abiraterone, enzalutamide, apalutamide and darolutamide) have proved efficient in metastatic castration-resistant Pca (mCRPC) patients as well as in hormone naïve patients, and actually in nonmetastatic diagnosis. The combination of these treatments with ADT highly inhibit androgen production pathways. They are prescribed to aged patients undergoing bone density loss after first-generation antiandrogen treatment. Specific recommendations for bone health management in Pca patients are currently lacking. To date, bone mineral density in patients treated with second-generation hormone therapy has never been assessed in a prospective study. This review aims at reviewing what is known about the impact of second-generation hormonotherapy on bone microenvironment.

Introduction

The incidence of osteoporosis in men increases exponentially with age. Nearly 25% of men over 60 will have an osteoporotic fracture (D’Amelio & Isaia 2015). One-third of hip fractures worldwide occur in men (Ebeling 2008), and 50% of these hip fractures occur before the age of 80. Unlike women, men are more likely to die within the year after a hip fracture. They are also less likely to return to independent living (Jiang et al. 2005). As known, age-specific hormonal decline plays a key role in the rapid loss of bone mass.

Prostate cancer (Pca) is the most common cancer among people aged 60 and 70. Between the age of 75 and 79, men are six times more likely to have a high-risk Pca than men aged 55–59 (Huynh-Le et al. 2020).
In 90% of cases, Pca is locally advanced or organ-confined at diagnosis (Yap et al. 2016). At this stage, patients are eligible for several therapeutic options (active surveillance, local radiotherapy or prostatectomy) (Lamers et al. 2017). Before having any treatment, 63% of hormone naïve men with prostate carcinoma have a T-score <2.5 (Smith et al. 2001). The T-score is defined as the difference between patient’s bone mineral density (BMD) and that of a young normal population divided by the standard deviation of the young normal population as follows: \[ T\text{-score} = \frac{\text{patient BMD} - \text{young normal mean BMD}}{\text{standard deviation of young normal population}} \].

Osteoporosis was defined by the World Health Organization in 1994 as a T-score lower than \(-2.5\), while osteopenia (low BMD) has a T-score between \(-1\) and \(-2.5\).

When cancer spreads outside the prostate, androgen deprivation therapy (ADT) is then initiated to decrease circulating testosterone levels, mainly through chemical castration rather than surgery (orchietomy). This stage corresponds to hormone-sensitive Pca (HSPC), also known as metastatic castrate-sensitive or hormone-naïve disease. After about 18–36 months, most patients develop resistance to ADT; as a result, they become castration-resistant Pca (CRPC) (Wadosky & Koochekpour 2016, Sumanasuriya & De Bono 2018) (Fig. 1). At this stage, patients usually have bone metastasis; the most common site of metastasis is vertebrae (Cereceda et al. 2003, Peng et al. 2017).

Androgen signalling remains the mainstay target in Pca treatment. Indeed, first-generation hormone therapies exclusively target androgen receptor (AR) translocation to the nucleus preventing downstream signalling. Second-generation antiandrogens enhance this mechanism (Rice et al. 2019), particularly acetate abiraterone (AA) which prevent androgen synthesis from testes and the adrenal glands. AA selectively inhibits CYP17 enzyme system essential for androgens production, known to be potent stimulators of tumour growth (Barrie et al. 1994). As to enzalutamide, it targets the androgen receptor (AR) signalling pathway by blocking the binding of androgens to AR, by inhibiting nuclear translocation of activated AR and by impairing the binding of activated AR with DNA (Schalken & Fitzpatrick 2016). Apalutamide is a competitive inhibitor of the androgen receptor. Like enzalutamide, apalutamide binds to the ligand-binding domain of AR with high affinity and minimal-to-no agonist activity (Clegg et al. 2012). Darolutamide is a unique nonsteroidal androgen receptor antagonist with low blood-brain barrier penetration. This novel therapy is structurally distinct from other antiandrogens with active diastereomers. It causes less severe toxic effects than apalutamide and enzalutamide because of its low blood-brain barrier penetration (Molilanen et al. 2015, Zurth et al. 2019).

As a result, second-generation hormone therapies are initiated in patients with bone loss related to age and ADT. Currently, Pca guidelines are poor in recommendations for monitoring bone health. To date, BMD in patients treated with second-generation hormone therapy has never been assessed in a prospective study. This article aims at reviewing what is known about the impact of second-generation hormonotherapy on the bone microenvironment.

### Androgen actions on bone

All life long, normal bone undergo remodelling for the skeletal integrity to be guaranteed and the phosphocalcic homeostasis to be maintained. Indeed, during childhood, more bone is produced. By the age of about 20 years old, peak bone mass is reached. Then, the amount of bone in the skeleton begins to decline slowly due to several
changes in bone cells. Bone density loss progresses rapidly in menopausal women (often between 3 and 5% a year for 2–3 years then 1–2% a year in the 5–10 years post-menopause). Ageing in men results in a progressive reduction of hypothalamic–pituitary–gonadal (HPG) axis function, decreasing testosterone secretion through both central and peripheral origins. From the age of 70, bone mass and bone calcium density keep decreasing. Age-specific hormonal decline plays a key role in the rapid loss of bone mass. The action of androgens on bone remains mostly unknown as the mechanisms by which androgens affect bone formation and cellular activities have mainly been assessed via preclinical models. Androgens promote the development and maintenance of skeletal structures (Nilsson et al. 2003). Higher AR expression was found in osteoblasts (OBL) from cortical bone compared to the cancellous bone with no sex-related difference (Colvard et al. 1989, Abu et al. 1997, Kasperk et al. 1997, Carson & Manolagas 2015). In the rodent model, AR inactivation induced a decrease in trabecular and cortical bone mass and, therefore, osteopenia in both the axial and appendicular skeleton (Yeh et al. 2002, Venken et al. 2006). At the cellular level, androgens stimulate the differentiation and proliferation of pre-OBL and inhibit apoptosis, whereas they inhibit bone resorption via RANK Ligand inhibition (Syed & Khosla 2005). In the rodent model, AR in osteocytes had a direct role in maintaining skeletal integrity and bone quality (Sinnesaal et al. 2012). As known, OBL are derived from bone marrow-derived mesenchymal stem cells (BMSCs). AR are also expressed in BMSCs. In vitro studies showed that BMSCs self-renewal is promoted in AR depletion through the upregulation of EGFR (Huang et al. 2013a). Furthermore, a loss of AR in BMSCs promote adipogenesis and suppress osteogenesis (Huang et al. 2013b). In addition to BMSCs proliferation, a lack of androgens implies first, an increase of osteoclasts (OCL) recruitment, secondly a longer lifespan for OCL and, thirdly osteoblastic and osteocytes apoptosis promoting bone loss.

**Androgen deprivation and bone loss**

ADT uses surgery or medicines to lower the levels of androgens in patients with Pca. The usual level of androgens is between 500 and 600 ng/dL. After castration, the level is <50 ng/dL. ADT results in decreasing trabecular BMD and increasing the risk of fracture (Smith 2002, PoulSEN et al. 2019). Indeed, during the first year following castration, locally advanced Pca patients experienced a 5–10% bone mass loss (Morote et al. 2011). Greenspan et al. showed that ADT caused an increase of bone remodelling markers (Greenspan et al. 2005). A recent meta-analysis in Pca patients who underwent ADT reported a significant decrease of BMD within three years follow-up (Dk et al. 2019). Five prospective studies with a total of 533 patients were included in this meta-analysis. Mean BMD difference relative to control group of BMD change was observed in lumbar spine (3.60, 95% CI, 6.72 –0.47, P = 0.02), femoral neck (3.11, 95% CI, 4.73–1.48, P = 0.0002). Furthermore, ADT administration increased the risk of fracture (Shahinian et al. 2005). Indeed, 5 years after diagnosis, 19.4% of those who received ADT had a fracture, as compared with 12.6% of those not receiving ADT (P < 0.001). Nonmetastatic Pca patients who underwent ADT without anti-resorptive therapy may suffer from a 21 to 37% increase in fracture risk (Shahinian et al. 2005, Smith et al. 2005). In a randomised controlled trial, Smith et al. assessed the effects of zoledronic acid – a resorption inhibitor- during ADT by LH-RH agonists for nonmetastatic Pca. It showed that mean BMD decreased by 2.2% in men receiving placebo, whereas it increased by 5.6% in those receiving zoledronic acid (Smith et al. 2003). Morote et al. Included 390 patients with Pca in their study (47.5% localised cancer, 41.3% locally advanced and 11.3% metastatic). If they had bone metastases, patients were excluded. 40.3% of patients had a radical prostatectomy, and 59.7% were treated with bicatulamide, 35.4% were hormone naïve. 42.9% of those who had received bicatulamide for 2 years suffered from osteoporosis. The occurrence of osteoporosis kept increasing; after receiving ADT for 10 years, 80.6% of patients had bone demineralisation (Morote et al. 2007). In another retrospective study, the same authors showed that BMD had decreased by 33% in nonmetastatic Pca patients treated with ADT (Morote et al. 2011). At the cellular level, ADT decreased OPG and increased the concentration of soluble RANKL in bone marrow, inducing osteoclasts activation, bone resorption and thus BMD decreases (Proell et al. 2009). AR regulates RANK/RANKL signalling in the bone microenvironment. ADT enhance this pathway inducing and acceleration of bone metastasis in a murine model (Takayama et al. 2017). In a model of Pca bone metastasis, the administration of zoledronic acid at ADT initiation prevented bone loss and subsequent relapse in bone (Ottewell et al. 2014).
Second-generation hormonotherapy validation in clinical trials and bone side effects

AA (Zytiga: approval granted on 5/11/2012) and enzalutamide (Xtandi: approval granted on 21/06/2013) are second-generation hormone therapy, considered standard of care in symptomatic or mildly symptomatic mCRPC. AA was also granted approval for early metastatic hormone-naïve cancers. The efficacy of post-chemotherapy (Docetaxel) AA was shown by the randomised, controlled Phase 3 study (COU-AA-301). In this study, 1195 mCRPC patients were assigned after receiving at least one line of chemotherapy (Logothetis et al. 2012). This trial showed that AA plus prednisone resulted in a 4.6 months overall survival increase compared with placebo plus prednisone (15.8 months vs 11.2 months, HR 0.74 and P = 0.0001) (Fizazi et al. 2012). Corticosteroids supplementation is used to mitigate adrenocortical insufficiency (Attard et al. 2012, Romero-Laorden et al. 2018).

One thousand and eighty-eight chemotherapy naïve CRPC patients were included in the COU-AA-302 clinical trial, a multi-center, randomised, placebo-controlled Phase 3 study. Patients received either AA plus prednisone (abiraterone group) or placebo plus prednisone (placebo group). At a median follow-up of 49.2 months, patients’ risk of death was 35.4% lower in the abiraterone group (HR: 0.65; 95% CI 0.54–0.77). Median overall survival was 4.4 months longer in the abiraterone group (34.7 months (95% CI 32.7–36.8) vs 30.3 months (28.7–33.3)) than in the placebo group (HR: 0.81 (95% CI 0.70–0.93); P = 0.0033) (Ryan et al. 2015). The most common grade 3–4 adverse events were cardiac disorders (8% in the abiraterone group vs 4% in the placebo group), increased alanine-aminotransferase (6% vs <1%) and hypertension (5% vs 3%) (Ryan et al. 2015). In the abiraterone group, patients’ median age was 71 (Rathkopf et al. 2014). COU-AA 301 and 302 studies did not include bone related-endpoint, however, no significant difference in bone pain was observed in patients receiving AA or placebo (Fizazi et al. 2012, Rathkopf et al. 2014). Similarly, in LATITUDE and STAMPEDE trials, no more bone side effects were observed under AA (James et al. 2017). In the IMAGEN study where nmCRPC patients were treated with AA and prednisone, 5.3% of patients had rib fracture (Ryan et al. 2018). In a prospective ancillary analysis of ABITUDE study, chemotherapy naïve mCRPC receiving AA+prednisone showed a progressive decrease of CTX and ALP levels throughout the study, indicating an inhibitory effect of bone formation and a reduction of disease extent (Santin et al. 2021).

As to enzalutamide, its efficacy was shown in patients who had previously received chemotherapy (AFFIRM clinical trial). One thousand one hundred and ninety-nine mCRPC patients were enrolled in this Phase 3 multicenter, randomised controlled trial. They had previously received at least one line of chemotherapy (Scher et al. 2012). Overall survival was prolonged by 4.8 months in patients from the enzalutamide group compared with those from the placebo group (18.4 months vs 13.6) (Scher et al. 2012). Adverse events were more common in the enzalutamide group (fatigue: 34% vs 29%, diarrhea (21% vs 18%), musculoskeletal pain: 14% vs 10%) (Scher et al. 2012). In this study, the patients median age was 69 (Fizazi et al. 2014). BMD remained stable over 24 months, under enzalutamide monotherapy in men with hormone-naïve Pca. However, bone remodelling biomarkers ALP and N-telopeptide were increased from the baseline to week 25 (Tombal et al. 2014). Patients receiving enzalutamide in ARCHES trial have experienced 6.5% of fractures (all grades) vs 4.2% with placebo (Armstrong et al. 2019), while 11.5% of fractures were observed in mHSPC patients enrolled in ENZAMET trial (Davis et al. 2019). Bone side effects related to enzalutamide was not reported in PROSPER and PREVAIL trials (Evans et al. 2016, Hussain et al. 2018).

Apalutamide, a competitive inhibitor of the androgen receptor. A total of 1207 men with nonmetastatic CRPC associated with a rising PSA underwent randomisation (apalutamide 240 mg/per day vs placebo: 806; 401) in this double-blind, placebo-controlled, phase 3 SPARTAN study. Median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (HR: 0.28 (95% CI 0.23–0.35); P < 0.001). More rash (23.8% vs 5.5%, hypothyroidism (8.1% vs 2.0%) and fracture (11.7% vs 6.5%) occurred with apalutamide than with placebo (Smith et al. 2018). The patients’ median age was 74 (Smith et al. 2018). In this study, patients were allowed bone-sparing agents (indicated for the treatment of osteoporosis at indicated doses and schedules). However, agents indicated for the prevention of skeletal-related events (SREs) in patients with solid tumours were prohibited (Smith et al. 2018). Apalutamide and ADT association induced 6.3% of fractures (all grade) in mHSPC in comparison with 4.6% in the placebo group (Chi et al. 2019).

The beneficial role of darolutamide was shown in ARAMIS study – an international phase III – in patients with nonmetastatic CRPC (Fizazi et al. 2019). In total, 1509 patients underwent randomisation (955 to the darolutamide group and 554 to the placebo group).
Metastasis-free survival was improved by 22 months compared to placebo (40.4 months vs 18.4 months). Patients median age was 74 (Fizazi et al. 2019). Grade 3 or 4 adverse events occurred in 24.7% of patients receiving darolutamide and in 19.5% of those receiving placebo. Yet, bone fractures did not occur more with darolutamide than with placebo (4.2% vs 3.6%) (Fizazi et al. 2019)

Second-generation hormonotherapy and bone microenvironment

In Pca, the balance between bone formation and bone resorption is altered because of the high tropism of Pca cells of the bone. The complex interplay between Pca cells and bone microenvironment leads to 'vicious circle' promoting bone metastasis. Indeed, metastatic Pca cells attached to osteoblasts to establish growth in bone (Shiozawa et al. 2011). Pca metastasis are also promoted through factors secreted by bone derived-cells particularly osteocytes (Sottnik et al. 2015). Approximately, 10% of newly diagnosed Pca patients presented with bone metastasis. This increased to 80% at advanced stages of the disease (Berruti et al. 2000, Bubendorf et al. 2000). Bone disease is associated with an increase of SREs inducing pain, reduced quality of life, and increased risk of death. The SREs has been used as a clinical endpoint which includes the detection of pathologic bone fractures, the spinal cord compression, and the need for orthopaedic surgery intervention or for palliative radiation to the bone. AA is not only associated with a significant survival, but also with better pain control, a delay in time to SREs development and in radiological skeletal progression. The AFFIRM study showed that enzalutamide administration induced a significant decrease in pain severity and had a beneficial effect on the rate of SREs in castration-resistant cancer patients with bone metastases (Scher et al. 2012). To our knowledge, to date no prospective study has evaluated the effect of these two second-generation hormonotherapy on bone mass. Few in vitro and rodent studies assessed the impact of these antiandrogen therapies on bone microenvironment. Human primary bone cells treated with non-cytotoxic doses of AA-induced inhibitory effect on OCL differentiation associated with a downregulation of osteoclastic marker genes (TRAP, cathepsin K and metalloproteinase-9). AA-enhanced osteoblastic differentiation, upregulated OBL specific markers (alkaline phosphatase (ALP), osteocalcin) and bone matrix deposition (Iuliani et al. 2015). This same study assessed bone turnover markers in 49 patients. Enrolled participants had metastatic castration resistant Pca with or without bone metastasis. AA administration at the dose of 1.000 mg daily with prednisone induced a significant decrease of serum carboxy-terminal collagen crosslinks (CTX) and an increase of ALP bone formation marker (Iuliani et al. 2015). The in vivo effect of abiraterone on BMD in addition to castration was examined using the murine model. Nakajima et al. reported that the addition of AA to castration did not affect BMD in the murine model (Nakajima et al. 2020). Old male mice treated with enzalutamide reduced the bone mass in the axial skeleton and high bone turnover (Wu et al. 2016). Mechanical strength in the axial skeleton was significantly reduced by enzalutamide (Wu et al. 2016). Furthermore, enzalutamide significantly decreased TGFβR2 (TGF-β type II receptor) in osteoblasts both in vitro and in patients samples (Su et al. 2019) TGFβR2 down-regulation was mediated by PTH1R via NR2F1 transcription factor (Su et al. 2019). Furthermore, loss of TGFβR2 in osteoblasts significantly promoted Pca bone metastasis (Meng et al. 2018). Thus, further experiments to understand the underlying mechanism of enzalutamide on bone metastasis are needed. No preclinical experiments of apalutamide (ARN-509) and darolutamide (ODM-201) on bone cells were found in the literature.

Discussion

Bone health is a critical issue in patients with Pca. Recent therapeutic advances, particularly with regard to the efficacy of second-generation hormonotherapy on OS, give hope for an extension of the life span of patients with Pca. These innovative therapies highly inhibit androgen production pathways. Thus, bone parameters definitely need to be monitored closely in patients treated with ADT. Our review highlights the scarcity of data assessing the impact of these hormone therapies on the bone microenvironment.

Skeletal fractures are a frequent and underestimated side effect of systemic treatment of Pca. Indeed, older age and long-term ADT have a negative impact on Pca patient’s BMD. In addition, chemotherapy, glucocorticoids and novel hormone therapy can also decrease BMD. Bone protective agents have then a dual role in SREs prevention and BMD improvement in Pca patients. A meta-analyses of 15 randomised trials revealed a significant fracture reduction in ADT patients treated with bisphosphonates (risk ratio (RR), 0.80) (Serpa Neto et al. 2012). Furthermore, BMD significantly increased at the lumbar spine by 5.6% compared to a loss of 1.0 in the control group,
<table>
<thead>
<tr>
<th>Molecule</th>
<th>Study</th>
<th>Indication</th>
<th>Median (min–max) age of patients</th>
<th>Previous androgen therapy deprivation</th>
<th>Associated corticotherapy/dose daily</th>
<th>Bone adverse events (experimental group vs standard care)</th>
<th>Ref/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>COU-AA-301</td>
<td>mCRPC (after failed chemotherapy)</td>
<td>69 (42–95)</td>
<td>Hormonal, surgery</td>
<td>Prednisone/5 mg</td>
<td>Bone pain: All grades: (27% vs 30%) Bone pain: All Grades: (21% vs 19%)</td>
<td>Fizazi et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>COU-AA-302</td>
<td>mCRPC (chemotherapy-naïve + prednisone)</td>
<td>71 (65–77)</td>
<td>ongoing androgen deprivation therapy</td>
<td></td>
<td>Bone pain: G1–2 (10% vs 13%) Osteonecrosis of the jaw: G1-2 (1% vs 0%) G3 (1% vs &lt;1%)</td>
<td>Rathkopf et al. (2014)</td>
</tr>
<tr>
<td>LATITUDE</td>
<td>mHSPC (with ADT + prednisone)</td>
<td>67.3</td>
<td>Up to 3 months of ADT with LHRH analogues or orchietomy with or without concurrent antiandrogens</td>
<td></td>
<td></td>
<td>Bone pain G3 (2% vs 2%) Osteoporosis G1-G4 (0% vs 0%) Fracture (0% vs 0%) (only AA+ prednisone patient) Rib fracture: any grade 5.3% Osteopenia: any grade 2.3% Spinal fracture: any grade 1.5% Wrist fracture: any grade 1.5% Osteoporosis: any grade 1.5%</td>
<td>Fizazi et al. (2019)</td>
</tr>
<tr>
<td>STAMPEDE</td>
<td>mHSPC (with ADT ± prednisolone ± radiotherapy)</td>
<td>67 (63–72)</td>
<td>LHRH-based (99%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IMAGEN</td>
<td>nmCRPC</td>
<td>72 (48–90)</td>
<td>ADT</td>
<td></td>
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</tr>
</tbody>
</table>

**Enzalutamide**

**AFFIRM**

mCRPC (post-chemotherapy) | 69.0 (41–92) | undergone orchietomy or were receiving gonadotropin-releasing hormone agonist therapy | | None | Musculoskeletal pain: Any grade: 14% vs 10% | Scer et al. (2012) |

**PREVAIL**

mCRPC (chemotherapy-naïve) | 72 (66–78) | Prior androgen for 88% of patients | | | Not reported | Evans et al. (2016) |

**PROSPER**

nmCRPC (chemotherapy-naïve) | 74 (50–96) | Prior ADT, or bilateral orchietomy. | | | Not reported | Hussain et al. (2018) |

**ARCHES**

mHSPC | 70 (46–92) | Previous use of ADT ≤ 3 months in 72% of patients | | | Fracture: Any grade: 6.5% vs 4.2% | Armstrong et al. (2019) |

**ENZAMET**

mHSPC (first-line therapy) | 69.2 (63.2–74.5) | ADT, LHRH analogues or orchietomy | | | Fracture: Any grade: 11.5 vs 6.5 G3 or 4 or G4: 2.7 vs 0.8 | Davis et al. (2019) |

**Apalutamide**

**SPARTAN**

nmCRPC (ADT treated) | 74 (48–94) | Surgery: Gonadotropin-releasing hormone analogue agonist; first-generation hormonotherapy ADT for no more than 6 months for mCSPC or no more than 3 years for localised PC prior AA, and enzalutamide and other ADT | | None | Fracture: Any grade: 6.3% vs 4.6% G3 or 4 or G4: 1.3% vs 0.8% Bone fracture: any grade 4.2 vs 3.6 | Smith et al. (2018) | Chi et al. (2019) | Fizazi et al. (2019) |

**TITAN**

mHSPC (with ADT) | 69 (45–94) | | | | | |

**Darolutamide**

**ARAMIS**

nmCRPC (chemotherapy-naïve) | 74 (48–95) | | | | | |
when denosumab was added in ADT setting (Smith et al. 2009). In the context of second-generation hormonotherapy, ERA 223 double-blind, placebo-controlled, phase 3 trial showed that fractures (any grade) occurred in 11% of patients who received AA (Smith et al. 2019). Likewise, 11.7% of patients experienced a fracture under apalutamide (Smith et al. 2018). The use of bone protecting agents, zoledronic acid or denosumab with second-generation hormone therapy remains usual. The addition of radium-223 to AA plus prednisone or prednisolone did not improve SREs-free survival in patients with CRPC and bone metastases. It was associated with an increased frequency of bone fractures than placebo (Smith et al. 2019). Post hoc analysis of recent Phase 3 clinical trials showed that bisphophonates or denosumab combined with AA or enzalutamide may increase survival (Saad et al. 2018). Recent clinical studies suggest that the addition of the bisphosphonate zoledronic acid and the RANK ligand inhibitor denosumab to these new therapies provide clinical benefits for patients with Pca and bone metastasis (Saad et al. 2018). It is important to point out that these clinical benefits are based on clinical trials post hoc analysis. Further prospective trials in real life population are needed to monitor bone mineral density and bone remodelling markers.

The older patients and the longer they receive hormone therapy, the higher their risk of osteoporosis. Indeed, the average age of participants in the pivotal second-generation hormone therapy trials is 70 years old (Table 1) besides; AA is indicated with low dose corticosteroids. Prolonged corticotherapy treatment often leads to osteoporosis. Thirty to fifty per cent of patients taking corticosteroids had fractures (Adler 2019). The effect of low-dose corticotherapy (5 mg, twice a day) taken with AA was evaluated in a retrospective study including 2267 patients (COU-AA-301 and COU-AA-302) (Fizazi et al. 2016). Exposure to such a combination was assessed at 3 months and 30 ≥months. Tolerance was good, adverse events were scarce (Fizazi et al. 2016). Rib and hip fractures were more frequent in patients receiving corticotherapy alone than in those receiving corticotherapy + abiraterone (2.3% vs 0.2%) (Fizazi et al. 2016).

In addition to the effect on BMD, ADT provokes a loss of 2–4% of lean body mass (LBM). Yet, LBM in men>70 years old decreased by 2.8% after 3 years of ADT (Smith et al. 2012). Moreover, decreasing LBM may contribute to greater risks for falls and fractures. Six months AA did not make pre-existing sarcopenia - age-related loss of muscle mass and strength- worse in patients with CRPC (Brondfield et al. 2012). Furthermore, a loss of 5.2% of skeletal muscle occurred early during enzalutamide treatment (Fischer et al. 2020). Sarcopenia was an independent risk factor of cancer-specific survival in patients with metastatic hormone-sensitive Pca, especially in younger patients (Ikeda et al. 2020). Assessing osteoporosis and fracture risk should be performed prior to ADT. DXA test (dual-energy X-ray absorptiometry uses a very small dose of ionising radiation to measure bone loss) is recommended prior to long-term hormone therapy treatment. Although BMD provides an estimation of osteoporosis, it is insufficient for predicting osteoporotic fracture risk (Wilkin & Devendra 2001). Indeed, several BMD-independent factors may contribute to fracture risk including age, sex, risk of falling, clinical medical history and other life-style factors (Brown et al. 2020). Fracture risk in Pca patients should be measured using FRAX tool and BMD assessment (Brown et al. 2020). Furthermore, patients should also be given advice about dietary and lifestyle choices such as regular resistance

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**Table 2** Second-generation hormonotherapy impact on bone microenvironment through preclinical models.

<table>
<thead>
<tr>
<th>Authors/years</th>
<th>Experiments</th>
<th>Antiandrogen</th>
<th>Model used</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iuliani/2015</td>
<td><em>In vitro</em></td>
<td>Acetate abiraterone (AA)</td>
<td>Primary human osteoblast/osteoclast</td>
<td>AA inhibits effect on OCL differentiation AA promotes OBL differentiation</td>
<td>Iuliani et al. (2015)</td>
</tr>
<tr>
<td>Nakajima/2020</td>
<td><em>In vivo</em></td>
<td>Acetate abiraterone (AA)</td>
<td>Cancer patient sera treated with AA</td>
<td>Decrease of serum CTX and increase of ALP in AA-treated patients</td>
<td>Nakajima et al. (2020)</td>
</tr>
<tr>
<td>Wu/2016</td>
<td><em>In vivo</em></td>
<td>Enzalutamide</td>
<td>Male mice</td>
<td>AA and castration did not affect BMD</td>
<td>Wu et al. (2016)</td>
</tr>
<tr>
<td>Su/2019</td>
<td><em>In vitro</em></td>
<td>Enzalutamide</td>
<td>MC3-T3 cells</td>
<td>Enzalutamide decreased TGFBR2 in osteoblasts</td>
<td>Su et al. (2019)</td>
</tr>
</tbody>
</table>
physical activity, daily calcium intake (1200–1500 mg daily) and vitamin D intake (800–1200 UI daily). They should be encouraged to stop smoking and alcohol abuse.

Little is known about the effect of second-generation hormone therapy on the bone microenvironment at the cellular level (Table 2). Recently, a unique novel 3D in vitro model reflecting bone microenvironment was developed. This relevant model is useful for new drugs testing in Pca (Samoto et al. 2020). With the progress of tissue engineering, new biological models will allow a better understanding of innovative therapies effects and the vicious circle between Pca cells and the bone microenvironment.

As we exposed previously, enzalutamide induced a TGFBR2 (TGF-β type II receptor) in osteoblast (Su et al. 2019). TGFBR2 gene silencing promotes bone metastasis. Primary osteoblast treated with bisphosphonate induced an increase TGFBR2 gene expression (Manzano-Moreno et al. 2018). Therefore, the TGFβ family may constitute an interesting track in the understanding of the second-generation hormone therapies in the crosstalk between malignant and bone cells microenvironment. Moreover, the exclusion of Pca patients with bone metastases from clinical trials does not allow the understanding of the effects of these new molecules on the bone microenvironment.

Conclusion

Patients with Pca benefit from a prolonged OS thanks to new hormone therapies. Thus, it appears necessary to assess the impact these new treatments have on Pca patients’ bone. Indeed, osteoporosis and its complications reduce patients’ quality of life, and for the elderly, it may end up life threatening. Thus, further preclinical and prospective studies are needed to better understand the impact of second-generation hormonotherapy on bone microenvironment.

Declarations of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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