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REVIEW

Bone-targeted Therapies for Prostate Cancer

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Introduction

Among solid tumors, the most common metastasis is seen in prostate and breast cancer patients. Approximately 90% of patients diagnosed with metastatic prostate cancer develop bone metastasis both at the time of the diagnosis or during the course of disease.[1] Skeletal complications may occur in patients with bone metastasis.[2] Nevertheless, SREs, such as pathological fracture are common in osteoblastic metastatic lesions due to bone instability.[3-5] Patients with bone metastasis in prostate cancer may annually experience more than 1 bone complications.[6] SREs are associated with increased mortality, pain, and low-quality life (QoL).[7-11]

Androgen deprivation therapy (ADT) causes a substantial reduction in serum testosterone level and is considered an essential weapon to combat tumor cells that consider androgens as growth factors.[12,13] Prostate cancer patients are generally old and may already have pre-existing bone disorders before initiating ADT. For example, in a study, the prevalence of osteoporosis in individuals over 50 years was ~19% in 348 males (mean age 55.4 years). In another study, in 618 patients who received ADT with newly diagnosed advanced prostate cancer (mean patient age 73 years), it was found that 80% of the patients had abnormal bone mineral density (BMD) at the beginning of the treatment.[14,15] Therefore, it is crucial to keep bone health at the center of all stages of prostate cancer treatment. The aim of patients with bone metastasis targeted therapies on preventing SREs, pain relief, and maintaining QoL.[16] Bone targeted agents, zoledronic acid (a bisphosphonate), and denosumab (receptor activator of nuclear factor kappaB ligand [RANKL] inhibitor) are approved for preventing SREs in patients with bone metastasis.[17-19] Moreover, Radium-223 dichloride (Radium-223), a radiopharmaceutical, is approved for the treatment of symptomatic bone metastases in castration-resistant prostate cancer (CRPC).[20] Denosumab is also approved for protection against ADT-associated bone loss.[19] Denosumab and bisphosphonates have also been investigated for their roles in preventing bone metastases.[21,22] Thus, understanding the possible role of denosumab and bisphosphonates in all stages of prostate cancer patients is mandatory to provide optimal care to prostate cancer patients.

This review evaluate the efficacy and safety data of bone-targeted therapies in prostate cancer patients with bone metastases and its molecular mechanisms identified to date.

Molecular Mechanisms of Bone Metastases

In healthy adults, the bone continuously undergoes remodeling to maintain structural integrity and minimize fractures.[23] Several types of cells, including osteoclasts (bone resorption cells), osteoblasts (cells producing and secreting osteocalcin and calcified matrix), and osteocytes (cells regulating osteoclast development), are involved in bone remodeling. Bone homeostasis is managed by a balance between these three cell types.[24]

ADT-induced reduction in estrogen levels results in irregular bone remodeling through the parathyroid-mediated activation of osteoclasts.[25,26] Circulating bone cells invading the bones alter the precise signal balance between the osteoblasts, osteoclasts, and osteocytes.[24] Tumor cells secrete factors stimulating the osteoclast activity or altering the osteoblast functioning. Thus leading to increased bone resorption (causes

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osteolytic lesions) or irregular formation of low-quality bone (may cause osteoblastic lesions); the latter being predominant in prostate cancer. Besides, osteolytic and osteoblastic lesions increase the risk of fractures and other SREs.[27-29]

Molecules produced during bone resorption or formationare used as biomarkers to determine the grade and assess the bone metastases in patients with solid tumors.[30-32] These markers include N-and C-terminal cross-linked telopeptides of type I collagen (both are markers for bone resorption), N-terminal peptides of procollagen Type I, and bone alkaline phosphates (BALP) (both are markers for bone formation).[23,30,33] An elevated BALP level may indicate bone metastasis associated with a poor prognosis.[31]

When osteoclasts start bone resorption, bisphosphonates are released that bind to farnesyl pyro-phosphate synthase in the osteoclasts and eventually leading to apoptosis.[18,34,35] Denosumab is humanized monoclonal antibody that has a different mechanism of action than bisphosphonates. It targets and binds to RANKL by preventing RANK activation on the surfaces of osteoclasts. Inhibition of RANKL-RANK interaction prevents osteoclast formation, functioning, and survival, thereby decreasing bone resorption.[29]

Hormone-sensitive Prostate Cancer and Bone Health

In nonmetastatic early stage prostate cancer, ADT is most effective treatment strategy. Treatment guidelines such as the European Society of Medical Oncology (ESMO) guidelines recommend ADT (e.g., gonadotropin-releasing hormone [GnRH] agonists or antagonists) in addition to surgery and radiotherapy to treat locally advanced prostate cancer. However, ADT is also recommended for high-risk localized prostate cancer and metastatic, hormone-sensitive prostate cancer (mHSPC).[36]

A 5-10% decrease in bone mineral density (BMD) frequently occurs within the first year after ADT initiation, leading to an increased risk of fracture correlated with ADT duration regardless of bone metastases.[12,13] A one of the cohort study using the data from the United States (US) CLAIMS database demonstrated that clinical fractures in males with nonmetastatic prostate cancer treated using GnRH-agonists increased by 21% than the untreated patients.[37] While some fractures are associated with bone metastases, a prolonged treatment elevates fracture risk.[37] Data obtained from New Zealand, Canada, China, and the United Kingdom (England) also demonstrated that fracture risk increased after ADT.[38-40] Denosumab and bisphosphonates may also protect bone health in non-metastatic hormone-sensitive prostate cancer (HSPC). Studies comparing zoledronic acid, alendronate, or risedronate with placebo as add-on therapy in patients treated with ADT have reported improvements in BMD in patients receiving bisphosphonate.[41-45] However, bisphosphonates have not been approved for this indication.[23] However, the RANKL inhibitor, denosumab, is suggested to prevent ADT-associated bone loss in males with an increased risk of bone fracture.[46] A one of the non-controlled study is evaluated 1652 male patients receiving ADT demonstrated that denosumab (60 mg) administration every six months reduced the incidence of new vertebral fractures by 1.5% during a 36-month follow-up.[47] The beneficial effects of denosumab compared to placebo and denosumab was superior than placebo looking at the parameters of age, duration, and type of previous ADT, BMD, T score, weight, body mass index, and bone resorption marker levels.[48]

Denosumab and zoledronic acid are indicated for preventing SREs in adults with bone metastases from prostate cancer especially mCRPC patients.[18,19] However, their effects on HSPC are not fully investigated. The CALGB 90202 trial assessed the early use of IV zoledronic acid (4 mg) every four weeks to prevent SREs in mHSPC. However, it was terminated early as no beneficial effect was observed for the first SRE over time.[49] It has been emphasized that more data analysis is needed for patients with decreased BMD at baseline, and studies on whether certain subgroups at the hormone-sensitive stage might benefit from zoledronic acid should continue.[50]

In some of the pre-clinical studies on hypogonadal mice injected with human prostate cancer cell lines demonstrated that androgen deprivation therapies might accelerate bone metastasis and also showed that when mice receive zoledronic acid, the incidence of bone metastases reduced.[27] Denosumab and bisphosphonates have a positive effect on survival in HSPC with the results of these studies. However, in a controlled, multi-center trial with 2962 patients having HSPC, zoledronic acid (4 mg) every 3-4 weeks with calcitriol plus docetaxel did not improve bone-related outcomes compared to the standard arm.[51] Similarly, in another study, adding zoledronic acid and celecoxib to standard therapy did not improve the survival of patients with metastatic prostate can-

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cer.[52] Data showing that adding zoledronic acid to standard therapy does not affect survival was also confirmed in a meta-analysis study in HSPC.[53] Nevertheless, findings obtained in studies with MRC PR04 and PR05 Clodronate and ADT have shown its overall survival benefit compared to placebo in patients with metastases ([HR]: 0.77; %95 CI: 0.60-0.98; p=0.032), however, this benefit was not demonstrated in patients without metastases (HR: 1.12; %95 CI: 0.89-1.42; p=0.94).[54] Furthermore, in the PR05 study, no significant benefit was demonstrated in bone progression-free survival in patients with metastases.[55] This lack of benefit led to the hypothesis that other mechanisms contribute to the development of bone metastases. It was observed that higher RANKL expression levels in aggressive metastatic prostate cancer cells compared to the cells obtained from the primary tumor support the hypothesis that osteoclast-mediated bone resorption stimulates the colonization and the progression of bone metastases.[56,57] Therefore, targeting more than one mechanism to effectively improve survival by treatment regimens is considered a more logical approach.

Castration-resistant Prostate Cancer and Bone Health

In HSPC patients, progression to CRPC was observed 2-3 years after initiation of ADT. This stage of the disease has a more rapid progression than the hormone-sensitive disease (median 18-24 months). SREs are associated with increased mortality in CRPC and bone metastases.[58] Zoledronic acid (4 mg IV every 3-4 weeks) and denosumab (120 mg SC every four weeks) are indicated for the prevention of SREs in patients with CRPC and existing bone metastases.[6,23,59] In a placebo-controlled trial, including 643 males with CRPC and bone metastases, zoledronic acid demonstrated fewer SREs (38% vs. 49% with placebo; p=0.028) and reduced the risk of general skeletal complications by 36%.[6] In a placebo-controlled, double-blind trial, including 1904 males with CRPC and bone metastases, denosumab treatment was superior to zoledronic acid in time to first SRE and time to second and subsequent SREs.[60] Time to first SRE increased from 17.1 months to 20.7 months (p=0.008). Furthermore, denosumab also delayed the second and subsequent SREs, which led to an 18% decrease in cumulative SREs.[60] Additionally, denosumab demonstrated a reduced risk of symptomatic skeletal events (SSEs) compared to zoledronic acid in posthoc analysis.[61] Skeletal pain is a complication of bone metastases with a significant effect on QoL associated with poor response to treatment.[11] In addition to their direct effects on bone health, denosumab and bisphosphonate treatment could improve bone pain.[62] In a pooled analysis of data obtained from three Phase 3 trials on patients with bone metastases due to CRPC, breast cancer, and other solid tumors, denosumab was found superior to zoledronic acid in terms of pain relief and intervention for pain.[62] Denosumab treatment also demonstrated delay in the onset of moderate/severe pain (median: 6.5 vs. 4.7 months; HR: 0.83; %95 CI: 0.76-0.92; p<0.001, and clinically meaningful increase in overall interventions for pain median: 10.3 vs. 7.7 months; HR: 0.83; %95 CI: 0.75-0.92; p<0.001). Compared to zoledronic acid, fewer patients treated with denosumab needed strong opioids or had clinically meaningful QoL worsening.

Radium-223 is a calcium mimetic that binds to the newly formed bone; its benefits in mCRPC were shown in Phase 3 Alpharadin study in patients with symptomatic prostate cancer (ALSYMPCA) and compared to placebo when added to standard-of-care.[63] The study was terminated as Radium-223 did not show a significant overall survival benefit from the results of the first interim analysis of the study (14.9 months with Radium-223 vs. 11.3 months with placebo; HR: 0.70; %95 CI: 0.58-0.83; p<0.001). Compared to placebo, Radium-223 significantly prolonged the time to first SSE (median: 15.6 vs. 9.8 months; HR: 0.66; %95 CI: 0.52-0.83; p<0.001). The randomized trial data confirmed the median overall survival of 16 months in an early access program using Radium-223 in patients with mCRPC. Moreover, this benefit was independent of the presence of symptoms.[64] In the Phase 2 trial, significant pain relief (p=0.035) was demonstrated within two weeks, and 71% of the patients had pain responses after eight weeks.[65]

It was suggested that denosumab and bisphosphonates might prevent the development of bone metastases in patients with CRPC; however, the evidence is insufficient. For example, it was reported that zoledronic acid treatment did not prevent bone metastases in both HSPC and CRPC trials.[22] In the Zometa European trial (ZEUS) of zoledronic acid (4 mg every three months) on 1443 males with high-risk, localized prostate cancer, no significant improvement was observed in bone metastasis-free survival after a median follow-up of 4.8 years. On contrast, in a double-blind, randomized, placebo-controlled Phase 3 trial in males with non-metastatic CRPC and high risk of bone metastasis, denosumab (120 mg every four weeks) sig-

nificantly improved the bone metastasis-free survival (HR: 0.85; %95 CI: 0.73-0.98; p=0.028) and prolonged the time to bone metastasis (33.2 vs. 29.5 months; HR: 0.84; %95 CI: 0.71-0.98; p=0.032). In addition, overall survival did not differ between the groups.[21] Nevertheless, denosumab is not indicated in patients without bone metastases as the difference in bone metastasis-free survival was not clinically meaningful.[66]

Safety Data on Denosumab and Bisphosphonates

When assessing the risk-benefit ratio, adverse events should be taken into account as there is a possibility that denosumab and bisphosphonates might be used longer in clinical practice than their historical investigation period.[50] Denosumab and bisphosphonates inhibit osteoclastic bone resorption and reduce the calcium release from the bone, associated with a risk of hypocalcemia.[67] In a study comparing denosumab (120 mg every four weeks) and zoledronic acid (4 mg every four weeks), hypocalcemia was observed in 13% of the patients receiving denosumab and 6% receiving zoledronic acid.[60] The higher hypocalcemia incidence observed with denosumab and zoledronic acid is consistent with their high anti-resorptive effects.[60,67] Hypocalcemia is most commonly observed early in treatment, stabilized over time, which does not increase with the increasing exposure time. Calcium and Vitamin D supplementation and serum calcium monitoring are recommended in zoledronic acid and denosumab treatment.[18,19]

Denosumab and bisphosphonates are also associated with an increased risk of osteonecrosis of the jaw (ONJ).[59] ONJ rate was reported to be 2.3% with denosumab and 1.3% with zoledronic acid (p=0.09).[60] The incidence of ONJ increases over time and is frequently observed in patients with poor oral hygiene and a history of dental extraction.[68] In an open-label denosumab trial, the incidence of ONJ was 3.8%. However, the ONJ rate was 8.2% at the end of the observation period, with a median follow-up of 5.6 years. In patients receiving zoledronic acid (4 mg every four weeks) and then switched to denosumab, the incidence of ONJ was 5.9% within five years, with the cumulative incidence of 2.2% up to 3.4 years. An overall analysis of the study (patients with breast or prostate cancer) reported 1.1% incidence of ONJ adjusted for patient-years in the first year of treatment, 3.7% in the second year, and 4.6% in the following year.[69] ESMO guidelines recommend preventive dental measures, good oral hygiene, and avoiding dental procedures before initiating treatment to reduce the risk of ONJ.[23]

Zoledronic acid is not metabolized and eliminated unchanged via kidneys. It is contraindicated in patients with severe renal failure (creatinine clearance <30 mL/min). Moreover, it should be used cautiously in mild-to-moderate renal failure, and dose adjustment might be necessary.[18] Non-renal monitoring or dose adjustment is necessary for denosumab in renal failure, including severe renal failure.[19,70] Nevertheless, individuals with severe renal failure are at risk of hypocalcemia and should be closely monitored.[19]

Historically, radiopharmaceuticals are associated with the risk of myelosuppression. However, the rates of myelosuppression are very low with Radium-223.[63] ALSYMPCA study demonstrated that Radium-223 might be tolerated better than the old-generation radiopharmaceuticals. The incidences of Grade 3 and 4 anemia, neutropenia, and thrombocytopenia were found to be 13%, 3.1%, and 6.1%, respectively.[1]

Current Practice with Denosumab and Bisphosphonates in Prostate Cancer

Proactive management of bone health is crucial for prostate cancer. However, many patients do not undergo bone density assessment in clinical practice. For example, in a Canadian survey study among 156 prostate cancer specialists, only 32.5% of the specialists reported that they routinely assess BMD before initiating treatment, and 36.6% reported that they assess BMD 1-2 years after treatment initiation.[71] There are several suggestions that denosumab and bisphosphonate prescription might vary with the specialty. Denosumab and bisphosphonate prescribing rates were investigated in 1971 patients with prostate cancer and bone metastasis in six European Union countries.[72] In the investigation, denosumab and bisphosphonate prescribing rates (78% vs. 60%, respectively) and the possibility of earlier treatment initiation were found higher (56% vs. 43%, respectively) when an oncologist rather than a urologist treats patients.

Optimizing the Use of Denosumab and Bisphosphonate in Clinical Practice

We know that denosumab and bisphosphonates could improve bone health in patients with any stage prostate cancer. However, the integration of these agents into disease management is limited with their licensed in-

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dications. It is also important to assess the benefit-risk profile of these agents. For example, although the risk of hypocalcemia in the early period, the incidence of ONJ increases in the late period.[67,68] The data comparing the efficacy of denosumab and bisphosphonates to prevent SREs in HSPC and early and late-stage mCRPC is lacking. Uncertainties about their initiation and dosing are common to all cancers associated with bone metastases; therefore, ESMO issued guidelines for bone health in patients with cancer.[23] These guidelines recommend that denosumab or zoledronic acid treatment be initiated when bone metastases are diagnosed and continued indefinitely throughout the disease course. However, the evidence demonstrated that this is not possible in clinical practice. Despite the controversial findings on protecting bone health in males receiving ADT, denosumab and bisphosphonates have a vital role in the treatment in the presence of osteoporosis, and their use is usually recommended by ESMO guidelines.[22,73-75] However, only denosumab is licensed in this indication.[46] ESMO guidelines also acknowledge that denosumab delays bone metastases in CRPC.[21,23] Although it is not licensed in this indication, its use is usually recommended. [19,23] In ESMO guidelines, there is no recommendation on Radium-223 use to maintain or improve bone health, except in the case of metastasis.

In addition to ESMO guidelines on bone health in cancer, there are recommendations in a series of guidelines of denosumab and bisphosphonate use in patients with prostate cancer.[36,76] On the other hand, the recommendations in these guidelines are inconsistent, which indicates that more data is needed on the timing of denosumab and bisphosphonate use in mCRPC. There is no recommendation on the optimal treatment duration and dosing in ESMO guidelines on prostate cancer. Although there are no recommendations on the use of denosumab or bisphosphonates in patients receiving ADT, it is recommended to monitor the males receiving long-term ADT for adverse effects, including osteoporosis.[36]

St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC) guidelines recommend that males with CRPC and bone metastasis receive an osteoclast-targeting agent to prevent SREs and SSEs. On the other hand, the timing, intensity, and treatment duration are unclear in these guidelines. Radium-223 is not recommended for routine use in the first-line treatment of patients with mCRPC.

European Association of Urology guidelines on prostate cancer recommends calcium and Vitamin D supplementation and denosumab or zoledronic acid in males with CRPC and bone metastasis to prevent bone complications. These guidelines also state that preventive treatment with low-dose bisphosphonates or denosumab may be considered in patients on ADT with fracture risk. It is also recommended to perform baseline and regularly on-going bone densitometry analysis on patients initiating ADT.

In a paper published by the International Society of Geriatric Oncology (SIOG), the need for focusing on bone health in older male patients with prostate cancer due to a continuous partial decrease in BMD caused by aging was emphasized.[76] The paper showed that despite the importance of agents such as denosumab and bisphosphonates in older patients with cancer, they are used inadequately. SIOG recommended that denosumab and bisphosphonates should be taken to prevent the development of osteoporosis in males over 75 years treated with ADT. In addition, the treatment should be initiated upon the detection of bone metastases to delay SREs and reduce complications. For safety, the age-related increased risk in conditions, including hypocalcemia, Vitamin D deficiency, and dental diseases should also be considered.[76] It is also recommended that the older patients' renal function be taken into account for treatment selection.

Cancer Care Ontario guidelines showed that the use of denosumab (60 mg every six months) reduces the risk of fractures in patients diagnosed with non-metastatic prostate cancer and receiving ADT. Denosumab (120 mg every four weeks) is recommended to prevent or delay SREs in patients with asymptomatic mCRPC.[77] Bisphosphonates at doses indicated for the metastatic bone disease are recommended in patients with mildly symptomatic or asymptomatic CRPC. No medication is recommended to prevent the development of bone metastases in patients with non-metastatic prostate cancer.[77] Guidelines stated that Radium-223 reduces SSEs, improves the patients' quality of life, and prolongs overall survival.[77]

The benefits of denosumab and bisphosphonates in patients with prostate cancer become more apparent as the disease progresses to CRPC and metastasizes to the bone. The effects of the new-generation hormonal agents (abiraterone and enzalutamide) on bone health should be considered. Both abiraterone and enzalutamide prevented SREs and delayed pain progression in patients with mCRPC.[78,79] However, whether these benefits mediate their anti-neoplastic effect or affect the interaction between tumor cells and bone is yet to be determined.[50] Data has also shown that

adding abiraterone to ADT in mHSPC may delay SSEs.[80] There is limited data on the effect of combined use of denosumab and bisphosphonates with these new-generation hormonal agents. Nevertheless, posthoc analysis of the data obtained from both arms of the COU-AA-302 abiraterone trial in mCRPC demonstrated that the overall survival improved in patients concomitantly receiving denosumab, zoledronic acid, or other similar agents.[81]

Conclusion

In addition to denosumab and zoledronic acid, Radium-223 showed efficacy in preventing SREs in mCRPC. Evidence showed that denosumab and bisphosphonates might also maintain bone health during prostate cancer. However, the supportive data on the practical integration of denosumab and bisphosphonates into the algorithms of prostate cancer management is insufficient. Information on the timing of denosumab and bisphosphonates in early prostate cancer and the duration of treatment with low-dose denosumab and bisphosphonates before switching to higher doses is also lacking. More data is needed to determine the relative benefits and risks of early treatment. The recommendations on the optimal integration of these agents into the management of prostate cancer should be clarified over time by the ongoing research. Consequently, evidence supports the use of denosumab and bisphosphonates to maintain bone health in cancer patients, provided clinicians take the adverse risk profiles of these agents into account.

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