

Bisphosphonates and innovative drugs in the prevention of skeletal complications secondary to metastatic prostate cancer

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ABSTRACT

Over than 80% of patients with locally advanced prostate cancer will develop bone metastases during the disease management. These metastases are often responsible for complications that impaired the quality of life, impaired the prognosis and increased the mortality by prostate cancer (PC). Two drugs are currently approved by the scientific community in the prevention of skeletal complications secondary to castration-resistant prostate cancer metastatic to bone (CRPCMB), zoledronic acid at a dose of 4 mg intravenously every 3-4 weeks and denosumab at a dose of 120 mg subcutaneously every 4 weeks. This aim of the preset paper was to review the current literature on the mechanism of action, efficacy, and safety profile of these two classes of molecules in the management of CRPCMB.

Key words: Bisphosphonates, denosumab, metastatic prostate cancer

INTRODUCTION

Prostate cancer is a very common cancer in men, it represent the second-most common cancer after lung cancer.^[1] This tumor, which was in the past in the most time was diagnosed at the stage of bone metastases, became a disease with preclinical discovery through screening (PSA). However, during their history, 80% of patients with locally advanced prostate cancer will develop bone metastases. These metastases are in most of the time responsible of complications that impair quality of life and prognosis, and increased mortality. Two classes of molecules are being developed for the prevention of skeletal complications secondary to castrate-resistant prostate cancer metastatic to bone (CRPCMB), bisphosphonates, targeting osteoclasts and a monoclonal antibody regulation the Receptor Activator of nuclear factor-kappa B ligand (RANK)-ligand pathway, denosumab.

NATURAL HISTORY OF PROSTATE CANCER

Current spectrum of bone disease in prostate cancer is represented by three clinical situations. The first situation was hormone-sensitive localized prostate cancer; the second: Was castration-resistant localized prostate cancer, and the third was castration-resistant metastatic prostate cancer. In the first situation, the aim of treatment was to prevent fractures secondary to hormonal therapy (castration). In the second, the goal of therapies targeting bone desorption was to prevent the occurrence of new metastases. In the third situation which constitutes the subject of the present review, the aim of treatment was to prevent complications associated with bone metastases.

RATIONAL OF USE OF THERAPIES TARGETING BONE RESORPTION IN CRPCMB

Despite the osteoblastic appearance of bone metastases in imaging, prostate cancer patients present an increase of urinary markers of bone resorption, indicating a significant osteoclastic activity.^[2] Increased osteoclast activity is significantly associated with an increased risk of bone

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complications, progression, and death. Therefore, the use of treatment targeting osteoclasts is a rational approach to reduce the risk of these complications.

PATHOPHYSIOLOGY

Number and differentiation of osteoclasts and osteoblasts are regulated by local and hormonal factors. The RANK/RANKL/osteoprotegerin (OPG) is an essential physiological regulator of osteoclastogenesis. RANKL is a transmembrane protein belonging to the family of ligands; Tumor necrosis factor (TNF), expressed by osteoblasts and stromal cells. The binding of RANKL to its receptor RANK expressed on osteoclasts and their precursors, promotes osteoclast differentiation and activity and survival of osteoclasts. Osteoprotegerin is a member of the family of soluble TNF receptors produced by osteoblasts and stromal cells, blocking the interaction between RANKL and RANK. Bone destruction associated with metastatic tumor infiltration is mainly mediated by osteoclasts, whose formation is stimulated by secretory molecule from derived from tumor secretion. During bone resorption, some released factors contribute to increase tumor growth and proliferation. The interaction between tumor cells and the bone microenvironment causes a vicious circle which increases bone destruction and tumor volume.^[3,4] The tumor osteolysis may be the cause of bone events such as mechanical complications (pathological fractures, spinal cord compression), bone pain, hypercalcemia, affecting the quality of life and survival. Skeletal complications related to prostate cancer have a negative impact on several levels: An increase in the cost of care for the patient (treatment of bone complications increased >2 times the cost to patients);^[5] a significant decrease in mobility (hip fracture is associated with 50% of motor impairment, 25% require nursing at home); a decrease in quality of life;^[6] and finally, a negative impact on survival (Men with PC without fractures survive more than 39 months).^[7]

TREATMENT OPTIONS FOR THE PREVENTION OF SKELETAL COMPLICATIONS SECONDARY CPRCMO

Bisphosphonates

Structure

Bisphosphonates are the first treatments developed to target osteoclastic bone resorption. Bisphosphonates are synthetic structural analogs of pyrophosphate (POP) in which the central oxygen atom has been replaced by a carbon atom. They therefore have a basic structure phosphate-carbon-phosphate (PCP) on which are substituted at the carbon atom to two-side chains R1 and R2. The PCP structure and chain R1 chelate calcium, bisphosphonates

confer their high affinity for hydroxyapatite bone matrix. R2 side chain is responsible for the inhibitory activity of bisphosphonates on osteoclasts.^[4]

Mechanism of action

Bisphosphonates are potent inhibitors of osteoclastic bone resorption with mechanisms of action and cellular molecular complex and variable depending on the bisphosphonate. They act by several mechanisms: They inhibit the formation and migration of osteoclasts as well as osteolytic activity, they induce apoptosis of osteoclasts, they regulate signal osteoblasts to osteoclasts, and they accumulate in the bone newly mineralized under osteoclasts. They inhibit osteoclast activity and thus the release from the bone matrix factors favoring continued lytic process and tumor growth and thus interrupt the vicious circle^[3,4]

Efficacy and safety

Several bisphosphonates have been developed in recent years and have authorization by the Food and Drug Administration (FDA) in the indications of malignant osteolysis, during hypercalcemia or for the prevention of bone complications in patients with malignant osteolysis. There are generally two classes of molecules, first-generation of bisphosphonates, such as colodronate, and the second-generation of bisphosphonates such as pamidronate, bondronate and zoledronic acid. The most potent molecule was the zoledronic acid, which has a 1000 times greater power than clodronate. Clodronate (2080 mg/d), is among the first molecules evaluated in randomized trials in this indication. This is a first generation oral bisphosphonate, which was assessed versus control arm in a randomized phase 3 including 311 patients with hormone sensitive metastatic prostate cancer. In the first published results in 2003, the primary objective was not achieved with clodronate. Clodronate improved survival without bone metastasis, but the difference did not reach the threshold of significance.^[8,9] Moreover, the results in terms of OS were recently published and showed a significant difference in favor of Clodronate, but this end point was only secondary in this trial. Pamidronate, a second-generation bisphosphonate, has been evaluated in two phase 3 clinical trials whose data and results were combined. In these two trials, patients with CRPC with bone pain were randomized to pamidronate (90 mg iv/3semaines for 27 weeks) vs. placebo. The primary endpoint was the reduction of pain or decrease in the use of analgesics. Another time, the results of this combined study showed no difference between pamidronate and placebo neither in terms of pain reduction nor in term of decrease of skeletal events.^[10] After the failure of these two molecules to confirm a significant benefit in metastatic PC, zoledronic acid the most potent bisphosphonate, has been tested in a Phase 3 trial vs. control; in this trial, 643 patients with CRPC with bone metastases were randomized to zoledronic acid (4 mg iv),

zoledronic acid 8 mg/4 mg and placebo every 3 weeks for 15 months. At 15-month follow-up, the incidence of adverse events (AEs) was significantly reduced in the ZA 4 mg iv arm: Only 33.2% of men in the zoledronic acid 4 mg group developed bone events vs. 44.2% in the placebo group. In addition, the zoledronic acid significantly increased the median time without skeletal events (423 vs. 321 days, $P = 0.047$) (primary end point). Median survival was also improved with zoledronic acid, but the difference was not significant. In addition, zoledronic acid significantly reduces urinary markers of bone resorption. In terms of toxicity, the most common AEs with zoledronic acid were: Fatigue, anemia, myalgia, fever, and swelling of the lower limbs. Regarding renal toxicity, only 3.3% of patients in the zoledronic acid 4 mg iv arm have developed a grade 3 decrease in creatinine, and no patient developed a grade 4 decrease in creatinine.^[11,12] Several limitations have been identified with this randomized trial: Skeletal events were vaguely defined: Pathological fractures, spinal cord compression, surgery or radiation to bone, therapeutic change in the treatment of bone pain; zoledronic acid is effective but is not specific in its effects: obvious effect on osteoporosis, possible effect on bone metastases secondary to prostate cancer.

Although zoledronic acid significantly reduces the incidence of skeletal events, more than 30% of patients will present skeletal events on this treatment, consequently the development or new molecules was performed.

Denosumab

Denosumab was the first targeted molecule developed in the prevention of osteoclastic bone resorption. The/RANKL pathway RANK/OPG was main regulator of osteoclastogenesis, and constitutes a very interesting therapeutic target in diseases characterized by bone resorption, such as tumor osteolysis. Denosumab is a fully human monoclonal antibody that specifically binds and inactivates RANKL and thus inhibits osteoclastic bone resorption.^[13] Denosumab at a dose of 120 mg subcutaneously plus placebo every 4 weeks was compared to zoledronic acid at a dose of 4 mg iv plus placebo every 4 weeks in a randomized controlled phase 3 in term of time to skeletal-related events (SREs) in patients with CRPC with bone metastases. The publication of results, showed that the primary end point was reached in favor of denosumab with a significant 18% reduction in the risk of SREs (20.7 months vs. 17.1 months, $P = 0.008$). This trial also confirmed the reduction urinary markers of bone resorption by the two molecules, and this decrease was significantly greater with denosumab. Furthermore, no significant difference in overall survival or in terms of time to progression was observed. Regarding the safety profile, the frequency of serious side effects was similar. However, there

were less acute reactions and less kidney complication with denosumab. There were moderately more osteonecrosis of the jaw (ONJ) (2% vs. 1%), and hypocalcemia with denosumab (13% vs. 6%).^[14] Several advantages in favor of denosumab: The monthly subcutaneous administration; The monitoring of the renal function is not required; Less acute reactions. Several issues are still under discussion: Cost effectiveness; Sequence between the two treatments; The concomitant use with chemotherapy and targeted therapies.

PRECAUTIONS BEFORE ADMINISTERING THERAPIES TARGETING BONE RESORPTION (NCCN 2012)

Before the administration of zoledronic acid, it is recommended to adjust the dose according to the creatinine clearance as shown in Table 1, and to ensure good renal safety during treatment with zoledronic acid, it is recommended to calculate the creatinine clearance before each treatment, and to stop treatment if creatinine increase of more than 5 mg up to the basal value (<14 mg/L). Regarding osteonecrosis of the jaw (ONJ), which is a serious complication of therapies targeting bone resorption, several risk factors have been implicated: Cancer; radiotherapy; corticosteroids; poor dental hygiene; poor nutrition, a history trauma, alcohol and smoking, coagulopathies, chemotherapy, and infection. The recommended precautions for the prevention of ONJ are: Having good dental hygiene, the decreased alcohol and tobacco use, the dental evaluation before starting treatment, avoid dental extractions during treatment; and encouraging patients to perform their dental hygiene.^[15,16]

INTERNATIONAL RECOMMENDATIONS (NCCN 2012)

Bone metastases are a common evolution of the locally advanced PC. Prevention of its complications is of capital importance. Two drugs are currently approved; zoledronic acid at a dose of 4 mg intravenously every 3-4 weeks and denosumab at a dose of 120 mg subcutaneously every 4 weeks. The denosumab has a confirmed advantage over zoledronic acid in terms of efficacy and safety, but the cost of this treatment is very high. Studies on the cost-effectiveness are needed to determine the most optimal strategy. Routine

Table 1: Adaptation of dose of zoledronic acid according to creatinine clearance

Clearance of creatinine	Dose of zoledronic acid
>60	4
50-60	3.5
40-49	3.3
30-39	3
<30	Not recommended

supplementation with calcium and vitamin D with both treatments is recommended. The optimal duration of treatment is unknown.^[15]

CONCLUSIONS

In prostate cancer, bone metastatic lesions can have negative effects on the quality of life. Multiple therapies have been developed to target bone-related complications for men with CRPCBM. Strong evidence supports the use of osteoclast-inhibiting treatment, the zoledronic acid, to prevent bone metastases-related fractures. More recently, phase III trials demonstrate that using denosumab in men with CRPCBM can more effectively prevent bone metastases-related fractures. Other interesting strategies are in the continuous development; as an example, the radium-223, Alpharadin, an alpha-emitting radioisotope, improved overall survival in men with CRPC and symptomatic bone metastases after treatment with docetaxel, according to a recent phase 3 clinical trial.^[17]

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