Osteoclast Targeted Therapy in Prostate Cancer

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Current standards of osteoclast targeted therapy in different stages of prostate cancer are reviewed, based on recent randomized trials with Denosumab for the prevention of skeletal related events, bone metastases and androgen deprivation therapy related fragility fractures.

Key words: Prostate Cancer, Bone, Targeted Therapy.

Based on regional registries, the incidence of prostate cancer in Romania has increased dramatically in the last decade (1) and it is very likely that at national level we are approaching the 22% of year 2008 new non-cutaneous cancer diagnoses in Europe (2). Despite the better awareness of men, the widespread availability of PSA testing and the high addressability towards urology consultation, the diagnosis is still in advanced stages for the majority of patients Overall, three out of four patients will eventually develop bone metastases. This translates into a significant impact on their quality of life and a major economic burden for the society. Until recently, non-chemotherapy treatment of bone metastases (BM) in hormone refractory prostate cancer (HRPC) was based on Zoledronic acid. Denosumab, a RANKL (receptor activator of nuclear factor kappa ligand) monoclonal antibody is a novel treatment option in this setting. The very recent evidence supporting this new treatment in prostate cancer is reviewed, including the prevention of bone metastases in high risk HRPC patients and also the prophylaxis of osteoporosis induced by long androgen-deprivation therapy.

Bone physiology

In adults, the total bone mass remains constant because of the equilibrium of two continuous processes: bone deposition by osteoblasts (OB) and bone absorption by activated osteoclasts (AOC). In this manner the normal toughness of the bone is preserved. The OB and OC are “living” in close dialog on the outer surfaces of the bones, refreshing the bone organic matrix. The OB secretes large amounts of alkaline phosphatase, which is a good marker of the rate of bone formation. The OC are tissue-specific macrophages which can be activated by local and systemic factors. When activated, they send out villus-like projections secreting acids and proteolytic enzymes that dissolve the bone salts and the organic matrix and liberate local growth factors. The main regulator of OC differentiation, activation and survival is the RANK signalling pathway (receptor activator of nuclear factor kappa B). RANK is a TNF (tumor necrosis factor) type receptor expressed by the OC. The OC is activated when the RANK-ligand (RANKL), expressed by OB and bone stromal cells, binds to RANK. OB produces also osteoprotegerin (OPG), a decoy receptor for RANKL, competing RANK (3). High levels of OPG leaves few “free” RANKL, so less RANKL-RANK binding and consequently, low rate of OC activation. RANKL expression is regulated by parathyroid hormone (PTH).

Bone changes in prostate cancer

Prostate cancer cells survival and growth is- at least for several years- androgen dependant. Androgen deprivation therapy (ADT) is standard for metastatic disease and -associated with radiation- for high risk non-metastatic patients. The aim of ADT is to lower the serum testosterone below 20ng/ml. This severe hypogonadism induces metabolic changes, a decrease in bone mineral density and an increased risk of fracture (4,5). According to the SEER and Medicare database in over 50.000 patients with prostate cancer, the risk of
fracture for those treated with ADT was 19.4 % vs. 12.6% for those who did not receive ADT (5). Thus, fracture prevention for men under ADT for prostate cancer is an important issue.

Prostate cancer metastases in bone are largely osteoblastic. The high OB activity is associated with increased OC activity, translated into an exceeded bone turnover state powered in a vicious cycle by the cancer cells metastatic to bone (Fig. 1).

**Fig. 1:** The vicious cycle of bone destruction when cancer cell interfere in the osteoblast - osteoclast communication (OB= osteoblast; OC = osteoclast; GF = growth factors, TNF = tumor necrosis factor, IL-1 = interleukin 1, TGF = transforming growth factor, IGF = insulin growth factor, PDGF = platelet derived growth factor, FGF = fibroblast growth factor; Ca = calcium).

**Osteoclast-targeted approved therapies**

In clinical practice, OC inhibition can be achieved with bisphosphonates (BPs) or with monoclonal antibodies against RANKL such as Denosumab (D-mab). For a prostate cancer patient with bone fragility due to ADT the aim would be the prevention of fractures, whereas for one already having bone metastases (BM) to prevent the skeletal related event (SRE), e.g. pain, fracture, spine compression or the need of surgery or radiation to treat these conditions. The potential activity of BPs or D-mab on the bone microenvironment or even their anti-tumoral effect have been raised by breast cancer studies and are “on the wave” in prostate cancer research.

BPs inhibit the formation of OC from precursor cells, decrease the OC attachment to the bone matrix and induces OC apoptosis (6). The in vitro potency of BP is related to the number of amino groups on the side chain: zoledronic acid (ZA) is 100 times more potent than pamidronate and at least 1000 times than etidronate and is the single BP approved in Romania for prostate cancer with BM (7).

Unlike the BPs, Denosumab- a fully human monoclonal IgG antibody against RANKL- has a long circulatory half-life (>1 month) and does not accumulate in bone. It has a very high affinity for human RANKL, blocking the vicious cycle of bone destruction by a sustained suppression of OC activity (there is no free RANKL to bind to RANK for activate the OC).

**Clinical data of osteoclast targeted therapy in prostate cancer**

A. **Targeting the bone metastases**

1. **Patients with bone metastases**

Based on the Zometa 039 trial on 643 patients, ZA was approved almost ten years ago as intravenous short time perfusion every 3 to 4 weeks to treat bone castration-resistant prostate cancer (CRPC) with asymptomatic or minimally symptomatic BM (8). In this trial, 4 mg of ZA versus placebo, every 3 weeks for 15 months was associated with a significant decrease in SREs (33.2 % vs. 44.2 %, p = .021) and a trend toward improved survival (546 days vs. 464 days, p = .09). Unlike in other solid tumors (e.g. breast cancer), the role of
BP in the prevention of BM remains undefined and other BP (like pamidronate or clodronate) failed to offer a benefit in this CRPC group (9, 10). However, in the MRC PR05 trial (11) on 311 castration-sensitive prostate cancer patients with BM, oral clodronate vs. placebo for a maximum 3 years was associated with a significant better 8-year overall survival (22 % vs. 14 %, HR 0.77, 95%CI =0.60-0.98, p=0.032). These results need confirmation and are in contrast with the lack of benefit seen of 5 years of oral clodronate vs. placebo for high risk localized prostate cancer with no evidence of BM (the MRC PR04 trial- see below). The CALGB 90202 is an ongoing trial searching for the potential benefits of OC targeted therapy (ZA vs. Placebo) in castration-sensitive metastatic prostate cancer.

In a recent randomized trial (12) on 1901 CRPC patients comparing 120 mg Denosumab vs. 4 mg ZA every 4 weeks, D-mab was superior to ZA in delaying the time to first on-study SRE (HR 0.82, 95 % CI: 0.71-0.95) and reducing the rate of multiple SREs (HR 0.82; 95 % CI:0.71-0.94). There were no significant differences in overall survival (OS), time to disease progression or osteonecrosis of the jaw (22 in the D-mab group vs. 12 in the ZA group, p=0.09). Hypocalcemia was more frequent in the D-mab than in the ZA arm: 13 % vs.6 % (p<0.0001), despite strong recommendation of daily supplemental calcium (≥ 500 mg) and D vitamin (≥400UI). D-mab is given subcutaneously, has no effect on renal function and therefore no need for renal monitoring and is not known to be associated with acute phase reaction (13).

II. Patients without bone metastases

a) In the Castration-resistant phase (PSA progression despite ADT)

The Zometa 704 trial was prematurely closed due to a low event rate after enrolment of only 398 patients of the 991 set as a target accrual. Median bone metastasis-free survival (MFS) was 30 months. PSA- velocity and baseline PSA independently predicted shorter time to first BM, MFS and OS (14).

The results of the Denosumab trial in this setting were reported one month ago (15) for 1435 men with CRPC, no BM but with high risk of developing them (PSADT≤ 10 months and/or PSA≥ 8ng/ml within 3 months prior to randomization). They were randomly assigned to 120mg D-mab s.c every 4 weeks vs. placebo. The median BM-free survival (primary end point) was 29.5 months for D-mab vs. 25.2 months for placebo (HR 0.85, 95%CI:0.73-0.98, p=0.028). Time to BM and time to symptomatic BM were also in favour of D-mab but there was no benefit in OS, whereas a trend toward a better progression free survival for D-mab was noted (HR 0.89, 95%CI: 0.78– 1.02, p= 0.09). The overall serious adverse effects were equal in both arms. However, osteonecrosis of the jaw (ONJ) was recorded in 4.6% vs. 0% and hypocalcemia in 1.7 % vs. 0.3% of the D-mab vs. placebo receiving patients. Six percent of the ONJ required bone resection, 64 % local debridement and curettage, whereas the remainders healed with oral rinses and antibiotics. This is the first trial in HRPC demonstrating that targeting the bone microenvironment prevents BM.

b) Castration-sensitive stage

The MRC PR04 negative trial mentioned above randomized 508 T2-4 prostate cancer without evidence of BM to 5 years of 2080 mg of orally daily clodronate versus placebo. There were no significant differences in the time of development of symptomatic BM, prostate cancer death or overall survival at 10 years.

The Zometa European Study (ZEUS) is an ongoing randomized trial testing the ZA ability of BM prevention in men having at least one high risk factor (among Gleason score ≥8, PSA ≥20ng/ml or N+) and treated with standard therapy with or without 4 mg ZA every 3 months for 4 years. The primary end point is the proportion of patients with at least 1 BM after 4 years of treatment.

B. Targeting the treatment related osteoporosis

Common definition of osteoporosis is a bone mineral density (BMD) T score of -2.5 or less. BMD is the usual surrogate measure of fracture risk hence the World Health Organization Fracture Risk Assessment (FRAX) calculator is a better predictor (free on line at http://www.shef.ac.uk/FRAX/). Long ADT (>6 months) is associated with BMD accelerated loss. Age ≥ 70 years, chronic glucocorticoid therapy (such as Prednisone) and excessive alcohol intake are additional factors for osteoporosis. It is recommended to perform a baseline Dexa-Scan for BMD assessment for every single prostate cancer patient presumed to receive long ADT.

Two positive fracture – prevention phase III randomized trials have been published recently (Table I), one with D-mab (16) and one with Toremifene (17), but yet none with BPs, despite the
proven efficacy of BPs on BMD increase. The design (active drug vs. placebo), study population (men receiving ADT, low baseline BMD or age ≥ 70 years), magnitude and the results of both trials were similar. The incidence of adverse effects were similar in the study and placebo arms.

Table I. Fracture Prevention Randomized trials in Prostate Cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>1468</td>
<td>D-mab 60 mg sc every 6 months for 3 years vs. placebo</td>
<td>6.7 % increased lumbar spine BMD</td>
</tr>
<tr>
<td>HALT138 (15)</td>
<td></td>
<td></td>
<td>62 % reduction of new vertebral fractures at 3 years (p = 0.006)</td>
</tr>
<tr>
<td>Toremifene</td>
<td>1389</td>
<td>Toremifene daily 80mg po vs. placebo</td>
<td>2 % increased lumbar spine BMD</td>
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<tr>
<td>G300203 (16)</td>
<td></td>
<td></td>
<td>50 % reduction of new vertebral fractures (p &lt; 0.05)</td>
</tr>
<tr>
<td></td>
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<td>Decreased breast pain, hot flashes, low density lipoprotein and triglycerides</td>
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Conclusion

Currently available data supports the use of ZA (4mg every 3-4 weeks, with creatinine clearance adjustment) to reduce SRE in bone metastatic CRPC but Denosumab was superior to ZA in delaying the SRE in this setting in one randomized trial. Denosumab has also been recently shown to prevent bone metastasis in high risk CRPC without proven bone involvement. Additionally, Denosumab significantly decreased the 3 years incidence of fractures related to long term androgen deprivation therapy for hormone sensitive prostate cancer patients older than 70 years and/or with low baseline bone mineral density.

References:


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