

Bone Metastases and Bone Loss Medical Treatment in Prostate Cancer Patients

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ABSTRAK

Kanker prostat adalah keganasan di bidang urologi yang paling sering bermetastasis ke tulang sampai 70% kasus. Penyulitnya berupa nyeri hebat, fraktur patologis, sindroma kompresi tulang belakang dan hiperkalsemia. Insidensi penyulit ini sekitar 46,1%, yang mengakibatkan peningkatan biaya perawatan dan memperburuk prognosis pasien.

Androgen deprivation therapy merupakan terapi baku kanker prostat yang telah bermetastasis. Terapi ini sendiri menyebabkan osteopenia atau osteoporosis.

Bifosfonat merupakan obat yang paling banyak dipakai saat ini untuk terapi metastasis tulang. Bifosfonat menghambat secara langsung aktifitas osteoclast dan secara tidak langsung melalui osteoblast. Denosumab merupakan opsi terapi terkini pada kasus metastasis tulang dengan efikasi yang lebih baik dari asam zoledronat. Efek samping denosumab sebanding dengan penggunaan bifosfonat.

Kata kunci: kanker prostat, metastasis tulang, bone loss, terapi.

ABSTRACT

Prostate cancer is a malignancy in urology with the highest incidence metastasize to the bone up to 70%. The incidence of skeletal related event (SRE) by 46.1% such as severe pain, pathologic fractures, spinal compression syndrome and hypercalcemia, with a consequence of higher inpatient care and worsen the patient's prognosis.

Androgen deprivation therapy (ADT) as a metastatic prostate cancer treatment itself causes an osteopenia or osteoporosis.

Bisphosphonate inhibits normal and pathologic osteoclast-mediated bone resorption by several mechanisms. Denosumab is the latest treatment option in bone metastases. Multi-study shows the efficacy of denosumab is better than zoledronic acid for SRE prevention. Adverse events between denosumab and bisphosphonate are comparable.

Key words: prostate cancer, bone metastases, bone loss, treatment.

INTRODUCTION

Prostate cancer is diagnosed in more than 670 000 men yearly worldwide.^{1,2} In the United States, an estimated 217,730 new cases in 2010, it is 28% of all cancer incidences in men.³ In developed countries, the majority of prostate cancers are found at an early stage as much as 75%, even in the U.S. by 95%. Indonesian Society of Urologic Oncology (ISUO) data shows during the period

2006-2010 there was stage 4; 490 patients (50.5%) of 971 prostate cancer patients.⁴ In Hasan Sadikin Hospital in the period 2004-2010 found 57% of cases are still organ confined and locally advanced, the remaining 43% of 320 cases were advanced stage cases. Fifteen percent of patients suffering from pathological fractures.

Prostate cancer is a malignancy in urology is the largest cause of bone metastases 65-

75% compared to the other malignancy.^{5,6} Complications of bone metastases=Skeletal Related Events (SRE) causes immobilization of the patient due to severe pain, pathological fractures, spinal compression syndrome and hypercalcemia.⁵ SRE incidence about 46% in prostate cancer patients who affects the cost of patient care and worsening prognosis.

Androgen deprivation therapy (ADT) as the standard therapy of advanced prostate cancer caused health costs to be doubled compared without ADT. ADT itself, on the other hand, causes bone loss.⁷ This process can be termed as a cancer treatment-induced bone loss (CTIBL).⁸

From another study, osteopenia was found in 27% of normal men and 37% in the prostate cancer patients before ADT.⁹ After treatment with ADT, whether it be orchiectomy, Gonadotropin Releasing Hormone (GnRH) with or without antiandrogen was causing the rapid decline of Bone Mineral Density (BMD) of approximately 4% -13% yearly.^{9,10}

The purpose of this paper is to review the drugs used to prevent or reduce bone loss from prostate cancer metastases and ADT induced bone loss.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF BONE METASTASES

BMD in middle life will decrease approximately 0.5-1% per year.¹⁰ Risk factors for osteoporosis are: hypogonadism, family history of osteoporosis, vitamin D deficiency, low calcium diet, smoking, excessive alcohol and long-term steroid use.^{11,12}

Normal bone remodeling occurs continuously regarding the shape and bone repair, which is influenced by osteoclast and osteoblast.⁵ Osteoclast and osteoblasts communicate via local paracrine factors are: Receptor Activator of Nuclear factor κ B (RANK) and progenitor cell. RANK receptor (RANK ligand/RANKL) produced by osteoblasts and progenitor cell has a central role in the communication process. RANKL and RANK bonding induces preosteoclast maturation to osteoclast, which end result of bone resorption and release growth factors such as Transforming Growth Factor β 1 (TGF β 1).

Fibroblasts Growth Factor (FGF), Platelet Degradation Growth Factor (PDGF) and Insulin-like Growth Factor (IGF) stimulate the formation osteoblast.^{8,13} In order for bone formation and

resorption remain in the balance of osteoblasts and stromal cells also produce osteoprotegerin (OPG) which serves as a diversion against the RANKL receptor, so the bond does not occur RANKL to RANK and induction of osteoclast for apoptosis (Figure 1).⁸

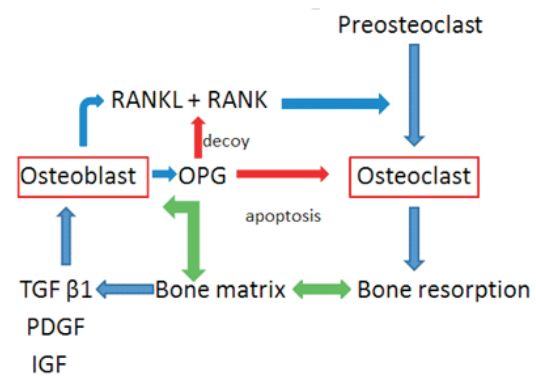


Figure 1. Normal bone cycle, adapted from Miller K⁷

Estrogen and androgen help to maintain bone balance. Estrogen plays a role in bone remodeling by inhibiting osteoclast. Androgens reduce bone resorption through aromatization of testosterone to estrogen. ADT disrupts the hormonal balance which bone need.⁹

Cancer cells metastasize through the blood or lymph will stick to the endothelial-specific bone marrow and migrate through the gaps between cells within 24 hours. Cytokines are found in the bone matrix is chemoattractant for prostate cancer cells.⁶ Factors such as bone morphogenic Bone Protein-4 (BMP-4) increases tumor cell adhesion to bone marrow endothelium. Adhesion and extravasation of cancer cells may also be facilitated by Protease-Activated Receptor 1 (PAR1). With the activation of PAR1, cancer cells will secrete Matrix Metalloproteinase (MMP). MMP causes basement membrane damage and facilitates the expansion of bone tissue invasion.⁶

When the process of osteolysis progresses, growth factors in the matrix such as TGF β , IGF2 is released, and causes activated osteoblasts in the area. Prostate cancer cells secrete BMPs, Prostate Specific Antigen (PSA), Parathyroid-related hormone (PTHrP) and the protease urokinase which have mitogenic effect on osteoblast (Figure 2).⁶

PSA involved in the case of predominantly osteoblastic. In addition, PSA will hydrolyze IGF-binding proteins that allow IGF-1 to stimulate osteoblast proliferation.⁶

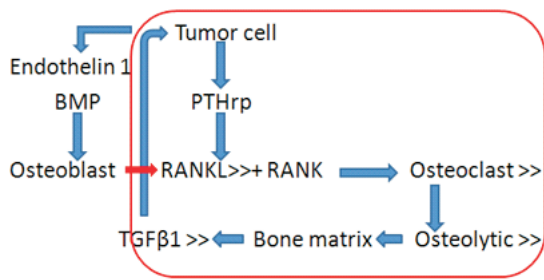


Figure 2. Vicious cycle of tumor growth; adapted from Saad F⁶

ADT INDUCED BONE LOSS

ADT causes testosterone deficiency secondary to impaired balance due to normal bone formation and resorption resulting in increased bone resorption.^{9,10}

Bone loss of a lumbar spine about 4.6%, femoral neck 3.9%, hip 9.6%, radius 4.5% in the provision of a first year of ADT.^{6,9} The relative risk of fracture associated with an increased dose and duration of ADT administration.¹² In general, the relative risk due to administration of GnRH agonist 1.21, pelvic bone fractures 1.76 and spinal 1.18 compared without ADTs.¹⁴

Morote et al. study showed that the increase in the occurrence of bone loss occurs mainly in the first year of ADT administration. Therefore, repeated BMD measurement should be done by the end of first-year.^{10,11}

BONE DENSITY MEASUREMENT

The modality that can be used to measure bone density is dual X-ray absorptiometry (DXA = densitometry) and quantitative CT-scan. However, the most often used is DXA.^{9,15} DXA was chosen because it can be done quickly and the X-ray dose that is lower than conventional X-rays.¹²

WHO classification considered normal BMD if T score of -1 or more, osteopenia -1 to - 2.5

and osteoporosis less than -2.5.⁹

Changes in bone density can also be measured by markers of bone metabolism. The process of formation and bone resorption can be detected from serum or urine. These markers can also be used to predict the occurrence of SRE, monitoring therapeutic efficacy and prognosis.

The marker can see a new bone formation such as alkaline phosphatase, osteocalcin and amino-terminal procollagen propeptides of type 1 collagen (PINP)¹⁶ or see the excess bone resorptionsuch as: N-telopeptide of type 1 collagen (NTX)¹², cross-linked N-terminal telopeptides of type 1 collagen (CTx), Carboxy-terminal pyridinoline cross-linked telopeptide of type 1 collagen (1CTP)¹⁷ and RANK.

The National Osteoporosis Foundation (NOF) recommends fracture risk assessment with the onlineWHO/FRAX® tool (<http://www.shef.ac.uk/FRAX/>).¹⁸

TREATMENT OF BONE LOSS

Calcium supplement of 1200-1500 mg/day in divided doses and vitamin D 400-800 IU/day prevents osteoporosis.^{12,19}

Estrogen administration can increase bone density and reduce the risk of fractures. Oral administration increases the risk for thromboembolism; intravenous administration is recommended. Another option is to use an estradiol patch, obtained from the study will be an increase of 3.6% bone density in the spine and 2.1% at the femoral neck. Side effects of estrogen are:gynecodinia 71% and gynecomastia 58%.¹²

Selective Estrogen Receptor Modulators (SERMs)such as Raloxifene and Toremfene also protect bone resorption by binding to the estrogen receptor on osteoclast and osteoblast.¹⁹ This drug will increase bone density of about 1%.

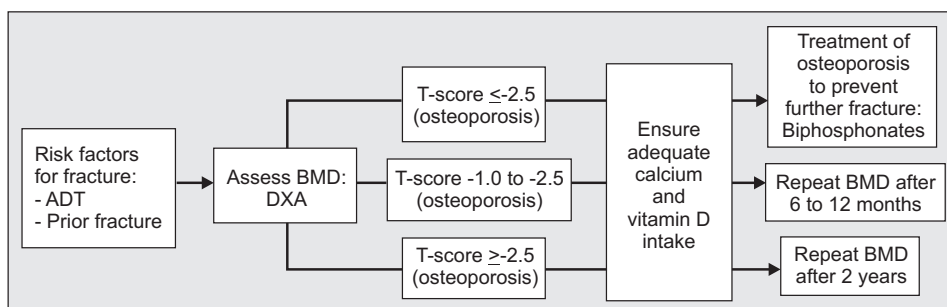


Figure 3. Clinical algorithm for assesment and treatment of ADT associated bone loss⁹

The use of nonsteroidal antiandrogen bicalutamide 150 mg per day as a single-agent increase BMD 2.5%, it is inversely proportional to the use of Luteinizing Hormone-Releasing Hormone (LHRH) was -5.4%.²⁰ Bicalutamide is a competitive inhibitor, inhibit binding of dihydrotestosterone to androgen receptor.¹²

Bisphosphonates is one of the most widely used today in the treatment of osteoporosis. Bisphosphonates inhibits bone resorption mediated osteoclast, so will prevent bone loss and high bone turnover. Bisphosphonates effect is influenced by carbon chain R1, which having a high ability to bind calcium. Carbon chains have been potential of antiresorptive.¹³ R2 chain modification by the addition of nitrogen would provide a stronger effect as in the zoledronic acid. Zoledronic acid is more potent than clodronate 100x and etidronate 1000x.¹³

Zoledronic acid will improve the effect of tumor cell growth inhibition and cell's apoptosis with through caspase pathway.²¹ It also has the effect of reducing the pain caused by bone metastasis.

Bisphosphonates per-oral is influenced by food and coffee, and therefore, better administered intravenously. Side effects of bisphosphonates such as: flu-like symptoms, acute renal failure (when given rapidly IV) and fracture of the jaw. Fracture of the jaw due to bisphosphonate administration predisposes by the presence of dental problems, steroids use and trauma.^{8,9}

Denosumab is a human monoclonal antibody (IgG2) developed to specifically target RANK Ligand; this is a new option in cases of bone metastases.^{22,23} It mimics the effect of endogenous OPG, so denosumab will prevent the bond between RANKL and its receptor (**Figure 4**), resulting in a decrease in osteoclast activity and bone turnover.²²⁻²⁵

Denosumab use was associated with increased bone mineral density at multiple skeletal sites in women receiving aromatase-inhibitor therapy for breast cancer.

Research shows that the denosumab better than zoledronic acid in preventing the occurrence of SRE.²⁶ The adverse events of denosumab were comparable to bisphosphonate.²²

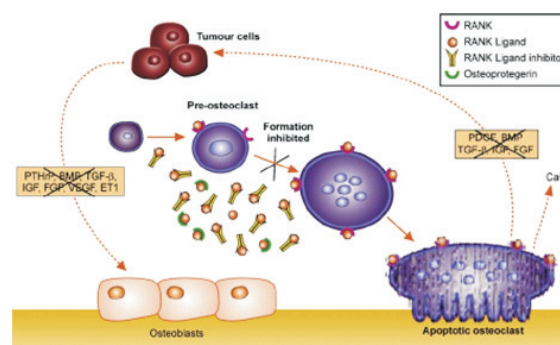


Figure 4. Inhibition of osteoclast-mediated bone resorption by a RANK ligand inhibitor²⁵

CONCLUSION

Skeletal complications are a major cause of morbidity for men with metastatic prostate cancer. Zoledronic acid and denosumab decrease the risk of skeletal complications in men with androgen-independent prostate cancer and bone metastases.

The reduction in risk of skeletal complications must be weighed against potential treatment-related adverse effects.

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