Zoledronic acid is the first bisphosphonat that confirms the efficacy in the treatment of bone metastases in prostate carcinoma. That is the most potent bisphosphonat up to date. Zometa is strong inhibitor of osteoclast activity.

Key words: prostate cancer, disseminated diseases, bone metastases, zoledronic acid

INTRODUCTION

The prostate carcinoma gives metastases through lymph and blood. Metastases in lymph nodes could be microscopic and difficult to detect, which represents a problem for correct estimation of the stadium of disease as well as for the adequate treatment, while bone metastasis, the most often metastases that spreads through blood, represent difficult therapeutic problem.

So, bone metastases of the prostate carcinoma, which re in 90% osteoblastic, bring to a heavy destruction of the bone system followed by severe pain, pathologic fractures, anemia, impaired mobility, spinal cord compression with paralysis.

It is understandable that bone metastases represent a huge therapeutic problem. Therapeutic options are: radiotherapy, endocrine and chemotherapy, orthopedic interventions, analgesic use and other medicaments, and in last decades - Bisphosphonates.

Bishopshonates are an important class of therapeutic agents, which are syntetic analogues of pyrophosphates that inhibit osteoclast - mediated bone resorption by strong incorporation in bone metabolism.

PHYSIOLOGIC CYCLES OF THE BONE REMODELING AND PATHOGENESIS OF THE BONE METASTASES

The bone system undergoes a constant, dinamic change, thorough the process of rebuilding and destruction. Cycle of bone remodeling is continual, and devided in few phases in which the bone reseration is effected by osteoclasts and bone formation is effected by mononuclears and osteoblasts.6,8,9

Nevertheless, at the existence of bone metastases, tumor cells produce substances that stimulate osteoclasts to increase their activity. It brings to an increase bone resorption with secretion of substances that stimulate tumour cells, perpetuating the cycle.

At this way, the "cycle vicious" is formed.

Huge disorder cause skeletal complications, such as: pathologic fractures, spinal cord compression, hypercalcemia of malignancy, local and generalized bone pain, impaired mobility and bone narrow insufficiency. All complications demand additional therapeutic options, often as radiotherapy and surgery.

Bisphosphonates are, as we have already said, incorpo rated in bone metabolism powerfully. The exact mechanism of their activity is not yet completely known, but we can be certain that they reduce osteoclast activity and hypercalcemia which is a result of the pathologic bone destruction.

All types of bisphosphonates consist of core, which is analog of pyrophosphates, and some of them have an imidosol ring with one, and Zoledronic acid - Zometa, two nitrogen atoms. Regarding unique structure, Zometa has demonstrated over 800 - fold greater efficacy than other bisphosphonates10.
Proposed mechanism of action include: inhibition of osteoclast maturation, functional suppression of mature osteoclast, inhibition of osteoclast recruitment to the site, reduction in the production of cytokines, eg, IL-1, IL-6 and inhibition of tumour - cell invasion and adhesion to the bone matrix.11,12,13,14,15

THERAPEUTIC EFFECTS OF THE ZOLEDRONIC ACID

Patients with bone metastasis of prostate cancer represent serious patients where only palliative therapy is possible, with especially short effect at the carcinomas with the high malignant potential.

A hormone therapy, which has a generalized effect on those patients, provide a good response in approximately 80-85%. During the hormonal sensitivity of carcinoma the effect on the metastasis is convenient, but less than at the primary tumour. At the beginning of hormonal resistance, the clinical manifestations of metastases are very prominent, mostly those in the bone. All further therapeutic treatments have even more momentary character with no important effect on survival but aiming to increase the quality of life.

The criteria for efficacy estimation of some drugs, even bisphosphonates, are adapted to this phase of disease. The term “skeletal events” is introduced, through which is indirectly concluded about efficacy of the medication. Those Skeletal include: pathologic fractures, spinal cord compression, need for bone surgery and radiation therapy of the change of present therapy. Beside the frequency of skeletal events, the important parameters of efficacy are: level of bone metabolism marker in urine, as well as in serum, impact on pain and bone density.

Based on these criteria the study P 039 was performed. It was phase III trial, which involved 422 patients, who were randomised to receive either Zometa or placebo11. All patients had hormon refractory prostate cancer with bone metastases. Zoledronic acid (Zometa) is administered parenteraly, 4 mg in 100 ml 5% dissolved glucose or 100 ml 0.9% NaCl, for at least 15 minutes intravenous. Adverse events occurred in small percentage as fever, anemia, nausea, vomiting, constipation, dispnea, confusion, insomnia, hypocalcaemia, diarea and stomachache.

Through the two year of monitoring there was a significant less patients with skeletal events in the group that received Zometa, teh in the control group. Zometa significantly delayed the time to first skeletal event by more than 5 months compared with placebo. Zometa significantly reduced the annual incidence of skeletal complications and also delayed the time to first pathologic fracture.

Objective parameters such as level of bone resorption markers in urine and bone formation markers have shown the efficacy of Zometa in prevention of bone destruction. Also, good efficacy is shown by measuring pain score in those patients.

By measuring the bone density is clearly shown that Zoledronic acid increases bone density. If we know that metastases, as well as antiandrogene therapy reduce bone density, it is clear that Zometa has a positive effect even during the use of antiandrogen therapy.

Researches have shown that Zometa has positive effect of prevention of bone metastases in direct and indirect ways.

Direct antitumour effect means the induction of cytotasis and apoptosis of tumour cells, as well as the inhibition of metastases and tumour angiogenesis. Indirect antitumour effect suggests the reduction in releasing tumour - promoting growth factors from bone matrix, as well as the reduction in adhesion of tumour cells to the bone matrix.12,15,16,17,18

CONCLUSIONS

Zoledronic acid is the first bisphosphonat that confirms the efficacy in the treatment of bone metastasis in prostate carcinoma. That is the most potent bisphosphonat up to date with safe, quick and simple administration. Zometa is strong inhibitor of osteoclast activity.

REZIME

ZOMETA U LEČENJU PACIJENATA SA METASTASKIM KARCINOMOM PROSTATE

Zoledronska kiselina je prvi biofosfonat čija je efikasnost potvrdjena u lečenju koštanih metastaza kod karcinoma prostate.

To je najjači biofosfonat sa sigurnom, brzom i prostom primenom. Zoledronska kiselina takodje ima preventivni efekat jake inhibicije aktivnosti osteoklasta, a takodje potpomaže i antitumorsko delovanje.

Ključne reči: karcinom prostate, metataska bolest, kostane metastaze, zoleodrnska kiselina.

REFERENCES


