ORIGINAL ARTICLE

Experience of bBisphosphonates aApplicationin a Rregional pProstate Ccancer aAdvance

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ABSTRACT

Bisphosphonatesarechemicalcompoundswhichpresentthe pyrophosphate analogue. Main mechanisms of bisphosphonates action on osteoclast are suppression of the maturation and the differentiation of its precursors, reduction of the osteoclasts life time, inhibiting the activity of osteoclasts. The paper presents the experience of zoledronic acid application in patients with the regional prostate cancer. With advance of the tumor process an increase in resorption markers was noted.

Application of anti-resorptive therapy with the use of latest-generation bisphosphonates in regional prostate cancer advance allows reduction of the intensity of bone metabolism according to the research data of bone metabolism markers. The use of zoledronic acid allows delay in the dissemination of tumor process ina bone according to the data of a skeleton isotopic study.

Keyw

Keywords: pProstate cancer, hormone therapy, resorption, zoledronic acid, metastases

INTRODUCTION

Bisphosphonatesarechemicalcompoundswhichpresent thepyrophosphate analogue.By contrast to pyrophosphate with P-O-Plink in the chemical structure, all bisphosphonates are characterized by the presence ofP-C-Plink. Besides, there are two radicals having different functions in the structure of bisphosphonates. The first radical is usuallyOH-group which enhances the physical and chemicalbinding of bisphosphonate with hydroxyapatite, while the second radical definesthe biological effect of bisphosphonate on cells (RussellR.G., 2011),(Russell R.G., 1999).This structural modification allows prevention ofcompound's enzymatic hydrolysis, provides biochemical resistance and does not inhibitthe specific binding and deposition of bisphosphonates in calcific bone matrix(RussellR.G., 2011).

By now,main mechanisms of bisphosphonate effect on the osteoclast are known.(Wada S., 2005).Theyarethesuppressionofosteoclastprecursor maturationanddifferentiationfromapoolofmultinucleate dcells, inhibitionofmechanisms of the osteoclastattachmenttoa bonesurface, shortening life time of osteoclasts, inhibition of osteoclast activity. Confirmation of the fact that bisphosphonates are capable to inhibitthe adhesion of some cells, mainly tumour cells, was obtained. Furthermore,the unique ability of bisphosphonates to inhibit the activity, migration and resorptive ability of osteoclasts, and, therefore, decrease the bone tissue

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resorption is realized. (Kanis J.A., 1994).It is very important that medicinal drugs of this group are characterized by long-continued activity which retains for a long time after treatment termination and is conditioned bytheir deposition in the mineral part of the bone matrix(Patel S., 1993).

Bisphosphonates can be taken by patients with hormonorefractive prostate cancer with bone metastasis to prevent bone complications.(Heidenreich A., 2010).The painresultingfrombonemetastasisisoneoftheworst complicationsof hormonehormone refractive prostate cancer. According to the data of minor open researches,bisphosphonates showed the high effectiveness that, in addition to the low incidence rate of side effects, make them a perfect medicinal drug for the palliative care.(Diel I.J., 2007)(Heidenreich A., 2001)(Heidenreich A., 2002).

It is ascertained that cancer cells produce a variety of factors which, directly or indirectly, activate osteoclasts to the bone resorption. Along with that, many cytokines and growth factors are released, including interleukine-6, which transforms β growth factorand others which, in turn, not only attract cancer cells to the bone tissue, butencourage their growth and proliferation. Thus, thepathologicbonedestructioncircle is completed.(KonstantinovaM. M., 2002).It is not hard

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to assume that with the advanceofprostatecancerandabsence ofmetastatic bone lesion,changes take place which favour the cancer cell disseminationinto a skeleton (Alasmari A., 2016).

Researchobjective. The objective of the study is to improve the effectiveness of hormone therapy through bone metastasis prevention with the use of zoledronic acid.

Substance andmethodsSUBJECTS AND METHODS

55Fifty fivepatientswithregional prostate cancer were under Urology Clinic careof I.M.Sechenov First Moscow State Medical University. The age of patients was67years (54 – 82 years old)[1]. The metastaticprocessinbonesisneglected on the basis of data of a bone tissue isotopic research. Majority of patients 51(92.7%) had moderately differentiated adenocarcinoma.

Patients received the hormone treatment with non-steroid42 (76.4%) and steroid3 (5.5%) anti-androgens in monotherapy6 (10.9%) or in combination with LHRH analogues 42 (76.4%) or orchiectomy 7(12.7%).

Patients received the hormone treatment with non-steroid42 (76.4%) and steroid3 (5.5%) anti-androgens in monotherapy6 (10.9%) or in combination with LHRH analogues 42 (76.4%) or orchiectomy 7(12.7%). AttheAt the timeofresearch34(61.8%) patients had the stable tumour stage. PSAlevel was0.3 (0.0-2.1) ng/ml. Its progression was determined in 21 (38.2%) patients, PSA level was20 (3.2-189) ng/ml.The median of the tumor stage advance was 35 months. Alongwiththat, more rapid tumor process progression was registered in patients without castration incomparisonwithpatientswho were subjected to medicationorsurgicalcastration medication or surgical castration (p=0.45)[2] 2.

In order to give a more accurate definition of thebone turnover status, the count of parathyroid hormone, osteocalcin, the level of β-cross-laps were determined for each patient.The level of parathyroid hormone was 39.5 (17.2-106.6) ng/ml, osteocalcin level was 20.3 (9.6-52.0) ng/ml, the level of β-cross-laps was 0.44 (0.12 – 1.41) ng/ml.In comparison of bone metabolism indicators inpatientswithstable and progressive tumorprocess, significant differences in levels of parathyroid hormone (p=0.542)[3]and osteocalcin (p=0.555) were not detected, however, with the tumor process advance the bone resorption marker (p=0.07) increase was noted. When tumor process stabilization,the level ofβ-cross-laps was 0.46 (0.17-1.6) ng/ml, against the background of advance it was0.36 (0.12-1.37) ng/ml.Thus, against the background oftheprostatecanceradvancesigns at the ascertained absence of a themetastaticskeleton bone lesion, we noted the increment of a bone tissue resorption marker. This supports the data ona bone tissue resorption increase by the direct or indirect stimulation bycancer cells.

In the tumour process advance, 7 patients were prescribed a zoledronic acid of 4 mg dose intravenously every 3 months in combination with other treatment modes. The other14 patientsdidnottakea zoledronic acid. Zoledronic acid is 100-1,000 times more active than pamidronate, its precursor. Pre-clinical studies had shown that it reduces the bone resorption and decreases the number of osteolytic and osteoblasticbone metastasis in experimental models of the prostate gland cancer.(Corey E, 2003). Zoledronic acid is a highly active bisphosphonate intended for intravenous injection which is registered to treat hypercalcemia caused by malignant tumors and bone metastasis. With the aim of lower jaw bone necrosis prevention, the oral cavity sanitation was preliminary carried out in all the patients,to whom the zoledronic acid was prescribed. (Spanou A., 2015)(Yoneda T., 2010).

The original level of bone resorption marker in patients who were prescribed a zoledronic acid was 0.44 (0.12-1.4) ng/ml. This indicator was 0.33 (0.12-0.97) ng/ml in those patients who did not received antiresorptive therapy. There were no significant differences originally between the groups (p=0.172).

At the control study after 3-6 months the level of a bone resorption marker when prescription of a zoledronic acid was 0.24 (0.12-0.3) ng/ml. In patients who did not take a zoledronic acid, the indicator was 0.53 (0.23-1.08) ng/ml.

Significant decrease of a bone resorption level (p=0.043)[4] was determined against the background of the bisphosphonate use. The level of β-cross-laps without correction didnot changesignificantly (p=0.463). This observation shows the high effectiveness of zoledronic acid in respect of bone resorption suppression in regional prostate cancer advance.

Further, the isotope analysis of a skeleton during the follow-up examination was carried out in patients with the prostate cancer advance and treatment

[1] Median is indicated, 5 and 95 percentile are in brackets
[2] Log-rank test is applied to compare
[3] Mann-Whitney test is applied
[4] Wilcoxon test is applied

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alternation. An average follow-up period of14 patients who did not take bisphosphonates was 16.6 months. Metastases in bones were detected in 3 patients from this group. The follow-up period of7 patients who were subjected to antiresorptive therapy ~~was~~were 32.6 months. Appearance of metastases was noted in one patient. No significant differences between groupswere revealed (p=0.73).

RESULTS ~~Findings and~~ DISCUSSION.

Physiological process of the bone metabolism takes a long time. Complete bone tissue regeneration takes approximately 10 years.(Kanis J.A., 1994).The pathological process progression is also extended in time and often does not have apparent clinical implications. This is typical for the prostate gland cancer. Use of state-of-the-art treatmentsof regional prostate cancer allows prolongation the disease recurrence progression time for some years. In our observation the prostate cancer advance median was35 months.

Against the background of continuing physiological bone metabolism, processes of bone density decrease are intensified with the age. Especially this process begins to declare itself after the age of 30-40 years. Equally, this is typical for women and for men. An increase in the number of patients with osteopenia and osteoporosis with age was demonstrated.

A group of men, which is included in our study, is characterized not only by an age and inherent to it factors of the bone mineral density reduction. In a described group of patients, the prostate cancer was proved by the histological examination. With an additional clinical study, the inoperable stage was determined. Taking into the account the clinical symptomatology, this group of patients was assigned the hormone therapy.

Thus, besides the age, a bone tissue was potentially affected by tumour growth factors. The immediate path of the penetration of tumour factors is confirmed by the presence of Batson venous plexus.

The first line for prostate cancer treatment is the hormone therapy. Methods of the hormonal therapy imply the suppression of testosterone synthesis by Leydig cells located in testes. Also, modern hormonal therapy implies blocking the contact of testosterone with receptors of target organs. First of all, cells of the prostate gland are considered. However, there exist other target cells for testosterone, located in other organs and tissues. This explains described side effects.

Use of the modern hormonal therapy agents is also able to influence the state of bone metabolism. Considering the suppression of the testosterone effects on the bone tissue, the gain of physiological processes reduction in the bone density should be expected.

At that it is also possible to determine more accurately the bone metabolism status, first of all the bone resorption status.

Markers of the bone metabolism, osteocalcin, β-cross-laps can be reliable indicators of the intensity of bone metabolism processes. They also can be applied to control the effect of hormonal treatment in patients with the prostate cancer. Use of bone metabolism markers is possible for comparison of the effectiveness of hormonal treatment and the state of bone metabolism. Comparison of osteocalcin and β-cross-laps indices makes it possible to present the balance of bone tissue synthesis and resorption processes in treatment and its effectiveness, besides clinical data.

One of indices of the calcium metabolism state is the level of the parathyroid hormone. The stimulus to its production is a decrease in the calcium concentration in the blood serum.

The analysis of bone metabolism in patients with locally advanced prostate cancer, receiving hormonal therapy, showed the increase in bone metabolism intensity. In general, the increase in indices of parathyroid hormone, osteocalcin and β-cross-laps bone resorption marker was noted. The intensity of bone metabolism in the described group can be the consequence of processes associated with age, the presence of a various intensity tumor process, as well as the effect of hormone therapy and its effectiveness.

The most apparent was the increase in the bone resorption marker β-cross-laps. This indicates a predominant activity of osteoclasts. At the same time, the increase in the osteocalcin level was noted. This indicates an increasing activity of osteoblasts, which produce osteocalcin. Thus, processes of synthesis and resorption of the bone tissue are in dynamic equilibrium, shifting under the effect of external factors. First of all, these are the tumour process and the conducted hormonal therapy.

The increase in the level of parathyroid hormone in the examined group of patients can bespeak the decrease in calcium in the blood serum due to age-related losses and intensive metabolic processes in a bone tissue. The relative decrease in the bone-synthesis marker - osteocalcin, apparently, depends on the inhibitory effect of parathyroid hormone on osteoblasts. The result is a predominance of the level of the bone resorption marker and the progressive decrease in bone mineral density.

Analysis of the parathyroid hormone, bone-synthesis markers - osteocalcin and bone resorption -

β-cross-laps indicates the existence of local and systemic levels of regulation.

When comparing the parathyroid hormone, osteocalcin and the resorption marker at the stabilization and progression of the tumour process, the predominance of the resorption marker was noted too. With progressing the tumour process against the background of anti-androgen flow, there takes place an increase in the pool of cells which are insensitive to androgens. Increase of the resorption marker in this group of patients can serve as the indicator of the indirect effect of tumour cells on a bone tissue. The result of this effect is an increase in the bone metabolism intensity with a balance shift towards the resorption. The resulting bone tissue becomes less compact. It can be assumed that the process of intensive bone metabolism with the formation of incomplete bone tissue can be a favourable basis for the appearance of metastatic process foci in bones.

The lack of reliable differences in parameters of parathyroid hormone and osteocalcin between groups with stabilization and progression of the tumour process against the background of the hormonal therapy of locally advanced prostate cancer can associated with the predominant effect of tumour factors on osteoclasts. Since bone metabolism is a dynamic process, the increase in the synthetic activity of osteoclasts can be secondary. Nevertheless, the activity of osteoclasts occurs to a lesser extent. Another factor of the prevailing effect of bone tissue resorption processes can be the increase in the parathyroid hormone level. In groups with stabilization and progression of the tumour process, no reliable differences in the level of parathyroid hormone were revealed. Thus, it can be assumed that the calcium exchange in these patients is less depends in a lesser extent on the activity of the tumour process. Nevertheless, the increase in parathyroid hormone activity in both stabilization and progression of the tumour process exerts an inhibitory effect on osteoblasts. This can be another explanation for the predominant effect of resorptive processes in the progression of the tumour process against the background of the hormonal therapy. At that, the hormonal therapy, aimed at blocking effects of androgens, continues giving a boost in the enhancement of physiological resorption processes of bone metabolism, characterized, in the first place, by a decrease in the density of bone tissue.

If present in the general outline processes occurring in men who receive hormonal prostate cancer therapy in the absence of proven metastases, then a bone tissue is in the state of its density decrease. This is characterized by the increase in the intensity of metabolic processes with a predominance of resorption. The dynamic equilibrium of synthesis and resorption takes place against a background of the physiological decrease in calcium. The reaction to this state is an increase in the production of parathyroid hormone, which inhibits osteoclasts and their synthetic activity. Parathyroid hormone also increases the re-absorption of calcium in the renal tubules, as well as the increase in calcium absorption in the intestine. This can be a major factor in the predominance of resorptive processes in patients with prostate cancer when determining a diagnosis in the absence of proven metastases.

The assignment of a hormone therapy even more strengthens the negative balance of calcium, reducing the intensity of synthetic processes in a bone tissue. When a negative balance of calcium, resorption processes are started. In its turn, as the response to this state, the increase in activity of osteoblasts happens. Dynamic equilibrium shifts, however, resorption processes still predominate. At that, the synthetic activity of osteoclasts is still restrained by the parathyroid hormone, which tends to keep the level of calcium in the blood within enough narrow frameworks. Sharp fluctuations in calcium of a blood plasma are accompanied by apparent and noticeable clinical implications.

When tumour process stabilization, the dynamic equilibrium described above with a predominance of resorption remains against the background of the hormone therapy. As time passed, this state leads to osteopenia and osteoporosis. The most significant clinical implication of a progressing decrease in bone tissue density is pathological fractures, which attract the attention of patients and clinicians.

In the case of progressing tumour process due to the hormone therapy ineffectiveness, even greater shift of the bone turnover dynamic process takes place. An increase in resorption takes place. At the same time, except for physiological processes, additional stimulation by effects of treatment with anti-androgens, takes place increase in the effect of factors, produced by the tumour. As in other cases, increase in resorption is a starting factor for the compensatory response from osteoblasts. Additional increase in the intensity of bone metabolism takes place. Enhancement of the bone metabolism against the background of tumour progression also occurs when the increased level of parathyroid hormone and continuing washing out of calcium. Parathyroid hormone continues to inhibit the synthetic activity of osteoclasts. Nevertheless, the intensity of bone metabolism becomes even greater. The end result is the formation of incomplete, less dense bone tissue. The risk of pathological fractures increases, and the probability of occurrence and progression of the metastatic process increases too. Moreover, the enhancement of the bone process happens due to an

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increase in a number of androgen-independent cells and enhancement of the tumour potential.

In our observation, the progression of prostate cancer was accompanied by an increase in bone resorption, which in this case can be considered pathological.

Thus, if the progression of the tumour process is detected against the background of treatment with anti-androgens, the question of changing treatment arises. This is dictated by the clinical manifestations of the disease, as well as the negative dynamics of prostate cancer markers. In addition to the previous indices, the negative dynamics of bone metabolism markers and parathyroid hormone can be revealed. They can bespeak the intensification of metabolic processes in the skeleton and the progression of the negative balance of calcium.

The decision of treatment tactics in this situation is conditioned by the treatment effectiveness of the underlying disease, minimizing of side effects and, if possible, reducing the risk of the negative effect on the bone metabolism state.

Virtually all drugs used to treat the prostate cancer, contribute to reduce the testosterone level. At present, the main strategy of treatment is the achievement of sub-castration levels of the male sex hormone. This inevitably contributes to even greater progression in reducing the bone tissue mineral density. Appearance of highly effective anti-androgens also causes a reliable blocking of testosterone effects not only at the prostate cell level, but also in other androgen-dependent tissues.

The need appears to apply drugs which can prevent enhancement of the pathological bone metabolism. This will allow reducing the risk of adverse clinical implications. First of all, reduce the risk of pathological fractures which complicate the underlying disease state.

Also in patients with the prostate cancer, there is a need to correct the negative balance of calcium. This state, it is possible to correct the assignment of calcium preparations. It is possible to control and change the dosage under the control of parathyroid hormone. The assignment of calcium preparations can reduce the parathyroid hormone concentration. Reduction of parathyroid hormone will increase the activity of osteoclasts and increase the synthetic processes in bones in response to increase of the resorptive activity. This will help to change the dynamic equilibrium in the direction of increasing synthetic processes and create the conditions for preventing bone resorption.

If under conditions of absence of a pathological process, assignment of calcium preparations is sufficient to slow down unfavourable processes in the bone tissue, then under conditions of the prostate cancer, hormonal treatment and, especially, its progression, additional assignments are required.

Application of modern, highly effective agents of reducing the pathological bone resorption of bisphosphonates allows reducing the pathological activity of osteoclasts.

The similarity of bisphosphonates with the main substance of bone tissue - hydroxyapatite makes them resistant to the chemical enzymatic hydrolysis and capable of being adsorbed on the surface of hydroxyapatite crystals. The ability of bisphosphonates to be deposited at the sites of a new bone formation has the fundamental importance in the effect of these preparations.

They are released from the surface of the newly formed bone, which are available to the extracellular fluid, but in places where the new bone is built, the bond becomes irreversible. It is maintained as long as the substitution of the old bone to to new one would not occur, that is about 10 years. However, whether the pharmacological activity of bisphosphonates remains is not known.

Main biological properties of bisphosphonates are: the ability to inhibit calcification and the ability to inhibit the bone resorption. Bisphosphonates can directly effect on osteoclasts and act indirectly on cells which model the activity of osteoclasts. The direct action of bisphosphonates on osteoclasts is confirmed by data of morphological studies. This process is characterized by a change in the expression of cytoskeleton proteins.

The fact was confirmed that bisphosphonates are capable to inhibit the adhesion of some cells, mainly tumour cells.

The reduction in the life of osteoclasts is probably associated with the toxic effect of bisphosphonates. There are data of experimental studies which prove the capability of bisphosphonates to induce a programmed cellular death of osteoclasts, both in norm and at the increased bone resorption. It is unknown whether this is the direct preparation effect on osteoclasts or mediated by other cells. A similar effect takes place in macrophage-like cells in vitro.

It was found that low concentrations of bisphosphonates determine their activity, which, probably, stimulates cell transduction paths with the help of receptors or binding sites on a cell. These structures are not identified to date. Since bisphosphonates penetrate the cell with the help of mechanisms of liquid or adsorptive pinocytosis, it is not improbable that there is an intracellular protein involved in the signalling cascade of reactions. Some bisphosphonates have the capability to block lysosomal enzymes, inhibit synthesis of prostaglandins, that indicates relationship of the bone

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resorption with these biologically active substances (КушлинскийН.Е., 2002).

Bisphosphonates differ in the mechanism of action. So clodronate is cytotoxic for osteoclasts, that are related to its effect on the bone resorption(Reitsma P.H., 1982). Pamidronate in doses, which suppress the bone resorption, does not have a cytotoxic effect. Pamidronate probably increases the amount of normal osteoclasts in the bone (Fitton A., 1991). Clinical concentrations of pamidronate do not directly affect the osteoblast activity or bone mineralization that is an important property of any drug for treatment of damages, characterized by the accelerated bone resorption. (Plosker G.L., 1994)Pamidronate acts via non-cytotoxic suppression of the function, migration and maturation of osteoclasts. The adsorption of pamidronate on the surface of hydroxyapatite crystals in the mineralized bone matrix reduces its solubility and makes it more resistant to the osteoclasticresorption. (Fitton A., 1991) The stronger bond between pamidronate and bone is probably conditioned by the presence of the nitrogenous part in its amino group. (Boonekamp P.M., 1986) Besides, the accumulation of pamidronate in certain parts of the bone, and, subsequently, with bone resorption, release, creates its high local concentration. (Elte J.W., 1986)Pamidronate in 100-fold smaller concentrations than concentrations depressing the function of osteoclasts suppresses involvement of osteoclast precursors in the mineralized matrix. This prevents the attachment of precursors of osteoclasts to the mineralized matrix, that, in its turn, blocks their subsequent transformation into mature, functioning osteoclasts (Fitton A., 1991).

Various bisphosphonates (except clodronate) inhibit post-translational modifications of proteins. Experimental data allow suggestion, that some bisphosphonates cause apoptosis through the formation of cross-bindings between proteins.

Bisphosphonates are widely used in the oncology: In the treatment of myeloma, bone metastases in a breast cancer and as a remedy to reduce hypercalcemia. (БеневоленскаяЛ.И., 2003)clodronate was used originally, then pamidronate and zoledronate. Under the effect of treatment, the bone resorption decreases, that is confirmed by the decrease in the level of calcium and corresponding bone markers, back pain decreases, the quality of life of patients improves. The prolonged action of the drugs is emphasized, that shortens the time of their administration, as well as the satisfactory tolerability.

In a number of cases an increase of the body temperature was noted just immediately after the drug administration, transient myalgia and arthralgia; anemia and thrombocytopenia, which did not require special intervention, developed in rare cases. (Body J.J., 1999)(Lipton A., 2000)

Analysis of the application of bisphosphonates in the oncology practice allowed drawing certain conclusions. (Hillner B.E., идр., 2003) The use of bisphosphonates provides the significant support to many patients with bone metastases, but does not increase the life expectancy of these patients. Using the example of patients with the breast cancer, the expediency of using bisphosphonates is shown on the basis of a decrease in the frequency of pathological fractures of vertebrae and compression of the spinal cord, the decrease in hypercalcemia.

~~This process can be controlled with the help of modern and accessible diagnostic tools (definition of a bone resorption marker).~~

In our work, we analysed results of the application of zoledronic acid preparations. This is the most effective bisphosphonate, widespread in the clinical practice.

Patients, who were assigned zoledronic acid, were characterized by an increase in the level of the bone resorption marker. Since the level of the bone resorption marker is the most sensitive index of the bone metabolism state, we used the analysis of dynamics of specifically this indicator in the future. In patients, who entered the comparison group, was also noted an increase in the resorption marker. Despite the relatively higher level of β-cross-laps marker in patients, who were assigned to zoledronicacid, no statistically significant differences between groups were detected. Thus, the initial state of patients, which included clinical and biochemical data, was the same.

In a control study of the bone resorption marker in patients with locally advanced prostate cancer, who was assigned to zoledronic acid against background of the hormone therapy, a statistically significant decrease in the bone resorption marker was noted. These data were obtained when pairwise comparison of initial and control indices. Thus, it is possible to judge the effectiveness of zoledronic acid application. Decrease in the intensity of bone metabolism takes place. First of all, this happens due to the osteoclasts activity oppression.

In the control group of patients who did not receive zoledronic acid preparations against the background of the hormonal therapy for inoperable prostate cancer, the level of the bone resorption marker was also defined more exactly. Terms of the control were comparable to the main group which received treatment with zoledronic acid preparations. Results of the control study of resorption markers in patients without zoledronic acid application indicate a

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tendency towards the increase in osteoclasts. Statistically significant differences between initial and control indices of β-cross-laps were not revealed. Thus, it is possible to bespeak the gradual progression of bone resorption processes in patients, who receive a hormone therapy for the prostate cancer. Metabolic processes in a bone tissue, which depend on the age, diagnosis, hormonal treatment, its effectiveness tend to progression.

This fact, an increase in bone metabolism, which tends to progression, is an indication for the use of highly effective inhibitors of the bone metabolism, representative of which is zoledronic acid.

We managed to trace the fate of patients from the groups described. In those of them, who were treated with zoledronic acid according to the control study data, the metastatic process in bones was ruled out. This conclusion was based on the data of the isotope study of the skeleton.

In the group of patients, who did not receive zoledronic acid in the treatment regimen, the subsequent study showed signs of a metastatic process. This fact can once again serve as the confirmation of the fact that the predominance of resorptive processes in bone tissue serves as a sign of not only progression of the tumour process, but also can be a precursor of appearance and development of prostate cancer metastases in the skeleton.

In 1889, Paget assumed that the growth of metastases is essentially similar to the growth of the "grain" in a certain micro-environment ("soil") and a clinically definable metastasis develops only in that case, if the grain and the soil are compatible. (МоисеенкоВ. М., 2004). The term "metastasis" was introduced by the French physician Joseph Claude Recamier in 1929 in "Recherches du Cancer" monograph. He, for the first time, presented anatomical evidence that the reason of metastases are cancer cells, which enter the bloodstream and are transported to body areas , which are distant from the original tumour. Even before Recamier, surgeons and anatomists noticed that boundaries of the tumour can expand through the cell colonization of adjacent tissues and lymph nodes, but it was believed that colonies of tumour cells in the more distant parts of the body arise independently. Recamier described the local infiltration, invasion of a cancer tissue in the walls of veins and secondary tumour growth in the brain in patients with the breast cancer.

The contribution of Recamier to the biology of metastasis earned him a place in the history of science, but did not help to improve the treatment of patients. In the case of breast cancer, he proposed a pressure bandage - apparently, to limit the spread of a tumour. But now it is known, that such an effect in practice promotes the transition of cancer cells into the bloodstream. Fortunately, this treatment has never been spread.

Metastatic spread is the transfer of tumour cells from the primary focus into other tissues, where they give rise to secondary tumours. The process of metastatic spreading is very complicated, very little is known about its biochemical mechanism. It is believed that metastatic spread reflects a violation of inter-cellular interactions, therefore, much attention is now paid to the study of features of normal and tumor cell surface. It is shown that the surface of tumour cells is rather strongly transformed, although not all changes are directly related to the process of metastatic spread.

At the present time, efforts of researchers are aimed at developing convenient animal modelling systems, with the help of which a metastatic spread process can be studied. Many works are devoted to elucidating the possible role of some proteases (for example, type IV collagenase), glycoproteins and glycosphingolipids of the cell surface in the phenomenon of metastatic spread. It is possible, for example, that a significant moment in the appearance of metastases is a change in the oligosaccharide chains which are included in the composition of cell glycoproteins (these changes are secondary with respect to changes in the activity of specific glycosylitransferase of glycoproteins). Understanding biochemical mechanisms involved in the metastatic spread process can provide a basis for developing more effective methods of the anti-tumour therapy (МарриР., 1993).

Recent studies of the metastatic spread showed that this process is, so to speak, a heavy multi-stage marathon, in which only a negligible fraction of tumour cells - less than one per 10 thousand cells, leaving the primary tumour - survives and gives rise to a new malignant colony (ЛансА. Лиотта, 1992).

The formation of metastases is usually due to the fact that circulating tumour cells find there an especially favourable "soil" for survival and growth, which can be provided by any hormones or growth factors which selectively stimulate tumour cells. Concentration gradients of certain proteins, which are secreted by target organs, can also attract tumour cells and encourage them to migrate from the bloodstream.

Clinical effectiveness of the modern anti-resorptive therapy application is shown up, first of all, in the decrease of bone metastasis occurrences rate in bones. Despite the lack of reliable differences between groups with respect to a number of metastasis occurrences, the observation follow-up period of patients who get the anti-resorptive therapy was significantly longer.

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CONCLUSION

Thus, in practically all patients with prostate cancer receiving the hormonal therapy, there is an increased probability of progression in reducing bone tissue mineral density. To define more accurately the intensity of metabolic processes in skeleton bones is possible through determining markers of the bone metabolism, for example, osteocalcin and β-cross-laps. Comparison of indices in dynamics makes it possible to define more accurately the hormone therapy effect on the bone metabolism intensity. Measurement of the parathyroid hormone level allows clarification of the degree of negative calcium balance evidence and compares it with the bone metabolism level.

Clinical and laboratory indices of the application effectiveness of anti-androgens and their comparison with indices of the bone metabolism allow making timely changes in a treatment. The reaction of bone metabolism serves as an additional method for more accurate definition of the treatment effectiveness.

Thus, application of the antiresorptive therapy with latest-generation bisphosphonates in regional prostate cancer advance postpones the dissemination of tumor process in a bone. The basis for prescription and effectiveness control can be more accurate determination of the bone resorption status and its dynamics. One more criterion of bisphosphonate application effectiveness can be reduction of bone metastasis occurrence rate at remote follow-up and increase of the survivability of patients.

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