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ANTITUMOR EFFECT OF BISPHOSPHONATES ON OSTEOSARCOMA IN SOME RECENT STUDIES

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Summary

In medical treatment of osteoporosis, various metabolic bone diseases and bone resorption caused by metastatic tumors, bisphosphonates have a very significant role. Lately, the problem of their antitumor activity, especially in combination with antineoplastic drugs becomes a very important area of concern.

Studies define that bisphosphonates have effect on growth inhibition, adhesion and proliferation, invasiveness of tumor cell lines; they induce apoptosis, inhibitory effects on osteoclastic bone resorption, reduce secretion of the local growth factors that stimulate tumor growth and positively interact with antineoplastics in extermination of tumor cells.

KEYWORDS: *bisphosphonates, osteosarcoma, in vitro and in vivo studies, antitumor effect*

ANALIZA NEKIH OD STUDIJA ANTITUMORSKOG UČINKA BIFOSFONATA NA OSTEOSARKOME

Sažetak

U liječenju osteoporoze, raznim metaboličkim bolestima kostiju, kao i resorpcije uzrokovane metastatskim tumorima kostiju, bifosfonati su se pokazali iznimno korisnim lijekovima. No pored navedenog, u posljednje vrijeme sve aktualnija je i njihova antitumorska aktivnost, posebice u kombinaciji s antineoplasticima.

Studije pokazuju da bifosfonati inhibiraju rast, povezivanje i invazivnost tumorskih stanica; potiču apoptozu, inhibiraju osteoklastičnu resorpciju kosti, smanjuju sekreciju lokalnih faktora rasta koji stimuliraju rast tumora, te pozitivno interferiraju s antineoplasticima u uništavanju tumorskih stanica.

KLJUČNE RIJEČI: *bifosfonati, osteosarkomi, in vitro i in vivo studije, antitumorski učinak*

INTRODUCTION

Bisphosphonates have very rare adverse reactions and drug interactions. Orally dosed, their absorption is very low, only 0.2 – 7%. After that, 20 – 80% of absorbed drug integrates into bone, and the rest is secreted through kidney elimination. The half-life of bisphosphonates is short, only 0.5 – 2h in the bloodstream. Once absorbed in the skeleton, in a higher range they are released with bone resorption. Pharmacokinetic studies show that the half-life of BPs is sometimes longer than the half-life in the skeleton and vary from 3 months to 10 years. The above mentioned indicates a powerful affinity for bone absorption and prolonged pharmacologically effect, long after blood level concentration were at the bottom. The side chains R1 and R2 in BP molecules could be various, their constitution determines the pharmacological activity, features of BP.

A number of existing *in vivo* and especially *in vitro* studies, reveal an anti-tumor effect of BPs. Moreover, the level of absorption is considerably, approximately several times larger in patients with tumors than in osteoporotic patients.

Therapeutic safety of BPs, selectivity in bone absorption and possible antitumor activity therefore are the area of concern, especially in tumor diseases like osteosarcoma. (1-5)

MATERIALS AND METHODS

The paper examines and compares several *in vitro* and *in vivo* studies with regard to the impact of bisphosphonates on tumors, especially on osteosarcoma, and their antitumor effect on tumor cell lines.

Criteria are based on a number of quotations and date of publication in verified scientific literature.

RESULTS AND DISCUSSION

Many recent studies reveal that inhibition of growth, adhesion, angiogenesis and cell invasion of tumors are directly effected by bisphosphonates (7-11). They stimulate apoptosis, inhibit osteoclastic bone resorption, reduce the local release of factors that stimulate tumor growth (autocrine, paracrine signaling), also they interact synergistically with other antineoplastic agents in extermination of tumor cells (12).

The antitumor activity of BP is affiliated with inhibition of prenylation of the structural proteins in signal paths within the cell, as Ras, Src, Rho and Rac proteins, considering inhibition of cell enzyme farnesyl PP synthase in the mevalonic path, with accumulation of isopentenyl PP (IPP) or induction of the ATP analogue (ApppI) (13-18).

Studies confirm that the presence of infiltrated osteoclasts or bone resorption intensity is in direct correlation with aggressiveness of osteosarcoma (19). Accordingly, therapy focused to inhibition of the osteoclastic activity becomes a matter of interest in possible curing of osteosarcoma. Lately, there have been numerous *in vitro* studies on animal and human cell lines and *in vivo* studies mostly on animal models. The studies show that nitrogen- bisphosphonates (N-BPs) in low concentration have influence on inhibition of adhesion of the tumor cells and reduction of their invasiveness throughout the extracellular matrix. A higher concentration shows an antiproliferative and proapoptotic effect. All the mentioned features of N-BP we could substantiate with several studies observing increases of DNA fragmentations in cells exhibited to N-BP, as well as arrest of the same in S-phase of mitosis (20-25).

N-BPs appear to have an inhibitory effect on matrix metalloproteinase (MMP), a very strong proteinase with ability to induce degradation of blood vessel basement membranes, and an important pre-requisite for tumor invasion and metastasis (26).

Novel studies refer to importance of a synergistic effect of BPs with antineoplastics. Therefore, the question is imposed on their concurrent application in patients with osteosarcoma. There are many unsolved problems in consideration of these issues. Lack of serious clinical researches on human population is one of the major sources of the problem, probably due to the low incidence of osteosarcoma in human population. Besides, there is a problem of dosage and application, as well as pharmacological dose efficiency (27-31). The aforesaid is a serious problem because studies revealed that osteosarcoma cell lines exposed to long-term low doses of BP against those non-exposed, in repeated proceedings with much higher doses showed up resistance (32).

One of the objects of examinations, for the purpose of improving the therapy is a combined introduction of bioactive molecules as osteoprotegerins. These molecules have properties of inhibition RANKL and essential role in pathophysiology of osteosarcoma. In this sense, also the introduction of antibodies on RANKL, RANK receptors and M-CSF is exhibited as an option for the purpose of palliative therapy of osteosarcoma (33, 34)

A very high affinity for bone is extremely important for their pharmacological effect on osteosarcoma. In some of *in vivo* analysis, as a result of limited distribution, short half-life in blood circulation, BP has not showed efficiency, especially in tumors of soft tissues despite their significant antitumor properties (8, 35). This fact throws a shadow on many *in vitro* studies that have been published lately on this issue for the reason of maintaining a constant, pharmacologically efficient concentration of BP in the microenvironment of tumor cell lines.

It is interesting to point out that statins like BP posses the ability of inhibition of enzymes in the mevalonic path and better distribution in soft tissues, so their antitumor effect becomes an of recent considerations.

CONCLUSION

The significance of the aforesaid researches is not only in revealing of the most efficient treatment for osteosarcoma and other bone tumors. Tumors of the breast, prostate gland and others often metastasize into bone causing serious complication of the disease including skeletal-related events (SREs).

All BP studies and their results are encouraging. Their anti-tumor effect especially comes to light in combination with antineoplastic agents, thus from the forthcoming and more exhaustive clinical studies we could expect some specific knowledge to be used for the purpose of optimizing therapeutic modalities and efficient treatment for osteosarcoma.

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