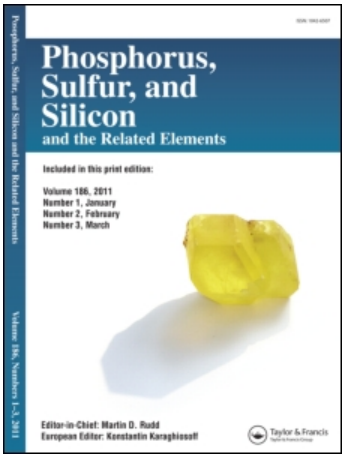

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EFFECTIVENESS OF AN EARLY OSTEOPROTECTIVE ADMINISTRATION OF BISPHOSPHONATES AGAINST TUMOR INDUCED OSTEOPATHY AND BONE METASTASES. EXPERIMENTAL FINDINGS

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Abstract. Using the rat model of tumor osteolysis after i. a. injection of tumor cells of the WCS 256 B systemic or local stimulation of bone metabolism (1,25 D_3, fracture trauma) enhances number and progression of tumor osteolysis. This increase can be reduced, when bisphosphonates (BPs) APD and Cl_2MBP are given before, with or after tumor cell injection. A direct inhibitory effect of the BPs on tumor cell proliferation can be excluded. In vitro tumor cell proliferation of the WCS 256 B can be enhanced, when bone conditioned media of fetal rat calvaria after stimulation with PTH are used. This increase can be abolished, when PTH is given together with Cl_2MBP but not with calcitonin. Our studies indicate that the prophylactic administration of BPs not only reduces the progression of tumor osteolysis but also impairs bone dependent tumor cell proliferation. These results are a strong argument for an early preventive administration of BPs in patients with a high risk for the development of bone metastases.

Key Words: bone metastases, bisphosphonates, osteoprotection

INTRODUCTION

As the majority of cancer patients die of the sequelae of metastases, it is clinically important to diagnose the metastases early and to treat or prevent the metastatic tissue and organ destruction. With respect to bone we have to answer the question whether an early pharmacological osteoprotection by osteoclast inhibiting drugs can retard or avoid tumor induced bone destruction and reduce the incidence of bone metastases.

EXPERIMENTAL STUDIES

When tumor cells of the Walker carcinosarcoma are injected into the aorta of rats, osteolytic tumor cell foci of the metaphyses of long bones develop, leading to complete osseous destruction and epiphysiolysis within 10 days. Histolocical examination shows that an abundant number of osteoclasts has been activated by tumor cells, which destroy the bone tissue in the vicinity to tumor cell foci. Systemic enhancement of bone metabolism for instance by 1,25 vitamin D_3 will enlarge the number and extent of osteolytic foci within the skeleton; local activation of bone metabolism by fracture trauma will increase the incidence of blood borne tumor cell foci at the site of trauma (Krempien et al. [4]).

The tumor induced bone destruction will markedly decrease when bisphosphonates are given to the animals showing a close dose dependency. Calcitonin however has been shown to be ineffective in this model of tumor osteolysis. Bisphosphonates when given prophylactically prior to the administration of tumor cells not only reduce the extent of bone destruction but also diminish the number of osteolytic foci within the skeleton (Krempien et al. [5]). However, the osteoprotective potential of the bisphosphonates decreases, when the therapy free intervall between administration of the compounds and tumor cell inoculation increases (Krempien et al. [3]). Our results clearly demonstrate that bisphosphonates have strong osteoprotective potentials and can prevent the development of bone metastases. These properties can be demonstrated both after therapeutical and prophylactical administration. These results are remarkable because bisphosphonates have been shown to pocess no direct effect on tumor growth. Therefore indirect effects must be involved.

We therefore proposed the hypothesis that bisphosphonates evolve their preventive effect on bone metastases by influencing the amount of growth factors, which have been shown to be locally released from the bone matrix by the activity of osteoclasts (Magro et al. [6], Orr et al. [7]). In order to the answer the hypothesis, we used the in vitro model of the 21 day old fetal rat calvaria and produced different kinds of bone conditioned media by stimulation of bone metabolism with PTH or inhibition by the bisphosphonate Cl_2MBP or calcitonin. Bone matrix resorption as measured by the

number of osteoclasts was markedly enhanced by PTH. When PTH was given together with Cl_2MBP this increase of osteoclastic activity was completely abolished, but calcitonin given together with PTH had no effect. Tumor cells of the Walker carcinosarcoma 256 B, which were grown in bone conditioned media of PTH stimulated calvaria, show a significant increase of proliferation in comparison to tumor cells, which had been cultivated in control media of unstimulated calvaria. Again calcitonin was not able to suppress the PTH dependent stimulation of tumor cell growth (Bu and Krempien, [1]).

CONCLUSIONS

According to these in vitro results tumor cell proliferation depend on bone metabolism and can be increased by stimulation or be decreased by inactivation of osteoclasts. Thus we draw the conclusion that the amount of matrix derived growth factors, which are available within the bone conditioned media determine tumor cell growth effectiveley. Bisphosponates but not calcitonin are capable of indirectly reducing tumor cell growth by influencing the breakdown of the bone matrix.

The therapeutic significance of the bisphosphonates is based on their rapidly beginning, selective and prolonged strong inhibition of osteoclasts (Fleisch [2]), which bestowes them a unique superiority over other osteoclast inhibititing drugs. There is now good experimental evidence that bisphosphonates after preventive and protective administration will reduce the development and progression of tumor osteolysis due to their obvious osteoprotective potential. The value of preventive clinical use of these compounds in tumor patients has to be seriously considered. The late diagnosis of osseous metastases means that valuable time is lost for antiosteolytic therapy with bisphosphonates.

In conclusion our experimental data represent a strong argument for an early osteoprotective administration of bisphosphonates to those patients at a high risk for developing bone metastases.

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