

PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Bisphosphonates inhibit breast and prostate cancer cell invasion

ArticleInfo		
ArticleID	:	3732
ArticleDOI	:	10.1186/bcr-2000-66695
ArticleCitationID	:	66695
ArticleSequenceNumber	:	98
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000-8-22 OnlineDate : 2000-8-22
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	1305822

Keywords

Bisphosphonates, invasion, bone metastases

Introduction

Breast cancer cells commonly invade bone, induce osteoclast activity and subsequent osteolysis leading to various detrimental clinical outcomes. BSPs have recently entered oncological practice as therapy for patients with metastatic bone disease. BSPs bind strongly to bone and in so doing inhibit bone resorption. There is both preclinical and clinical evidence that the BSPs may also have direct antitumour effects. *In vitro*, BSPs have been shown to induce apoptosis in myeloma cells, and to inhibit matrix metalloproteinase production by prostate cancer cells. Diel *et al* (see Additional information) reported that in the adjuvant setting, breast cancer patients receiving a BSP had a reduced chance of developing visceral metastases.

Aims

To determine whether BSPs have direct inhibitory effects on tumour cells in terms of induction of apoptosis, cell invasion and cell migration.

Comments

This interesting study attempted to elucidate possible further modes of action of the bisphosphonates (BSPs). These agents are rapidly becoming a major component of the treatment of bone metastases in patients with metastatic breast cancer or multiple myeloma. Although proven to have major effects on osteoclast-driven bone resorption, there is increasing evidence that the BSPs possess a more complex variety of biological actions. In particular, work by Diel *et al* (see Additional information) on the adjuvant treatment of breast cancer suggested that the BSPs may have direct antitumour effects. Although supported by some laboratory data, it is unclear whether this is in fact a real finding. Of two other studies of BSPs in adjuvant breast cancer, one found no impact of BSPs on development of non-

bony metastases, and the other actually found an increase in non-bony metastases. This study, whilst suggesting that BSPs can affect tumour cell invasion, could not identify the actual mechanism for this effect. Thus, a great deal more work is needed, both *in vitro* and clinically, in order for the full spectrum of activity of the BSPs to be elucidated. This may have important implications in determining the roles that the BSPs may play in cancer management.

Methods

Six different BSPs (clodronate, zoledronate, ibandronate, and three analogues of risedronate - one potent [NE-10244], one inactive [NE-58051], and one with a phosphate group substituted by a carboxyl group [NE-10790] were tested on two cells lines. The two cell lines were a human breast (MDA-MB-231) and a prostate (PmPC3) cancer line, both highly metastatic to bone. Treated and untreated cells were tested using a cell migration assay, a Matrigel invasion assay, a cell cycle/FACS analysis, an apoptosis assay and an analysis of matrix metalloproteinase (MMP) activity.

Results

Cell migration assay: none of the BSPs tested inhibited tumour cell migration. Matrigel invasion assay: the BSPs inhibited both breast and prostate cancer cell invasion, reaching 60-90% inhibition. The most potent inhibitor was zoledronate, and the least potent was clodronate. NE-58051 (inactive) had no effect. NE-10790 (carboxyl substitute) did inhibit migration. Zoledronate, the most potent of the BSPs, did not induce apoptosis in tumour cells. The BSPs did inhibit the proteolytic activity of the three MMPs tested (MMP-2, -9, -12). All the BSPs tested were equipotent in this regard. Interestingly the inactive analogue, NE-58051, also inhibited MMP activity but the carboxyl substitute, NE-10790, did not.

Discussion

BSP pretreatment of breast and prostate carcinoma cells inhibited cell invasion in a dose-dependent manner. The fact that the inactive analogue NE-58051 had no inhibitory effect, whereas NE-10790 (the carboxyl substitute) did have, indicates that the inhibitory activity of BSPs involves the R2 chain of the molecule. BSPs did not inhibit tumor cell migration at concentrations that inhibited tumor cell invasion, and they did not induce apoptosis in tumor cells. They did, however, inhibit the proteolytic activity of the MMPs. This effect was completely reversed in the presence of an excess of zinc. In addition, NE-10790 did not inhibit MMP activity, suggesting that phosphonate groups of BSPs are responsible for the chelation of zinc and the subsequent inhibition of MMP activity. In conclusion, this study indicates that the BSPs do have a direct effect in preventing cell invasion, with an inhibitory effect on the

proteolytic activity of MMPs. These results suggest that BSPs may have a role in the prophylactic treatment of patients with cancers that are known to preferentially metastasise to bone.

Additional information

Boissier S, Magnetto S, Frappart L, Cuzin B, Ebetino FH, Delmas PD, Clezardin P: **Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices.** *Cancer Res* 1997 **57**:3890-3894 ([PubMed%20abstract](#))

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