Journal of Bone Oncology 3 (2014) 25–35

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

The anti-tumour effects of zoledronic acid

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ARTICLE INFO

Article history:
Received 6 October 2013
Received in revised form
16 December 2013
Accepted 19 December 2013
Available online 15 January 2014

Keywords:
Zoledronic acid
Bisphosphonates
Apoptosis
T-cells
Angiogenesis
Antitumour

ABSTRACT

Bone is the most common site for metastasis in patients with solid tumours. Bisphosphonates are an effective treatment for preventing skeletal related events and preserving quality of life in these patients. Zoledronic acid (ZA) is the most potent osteoclast inhibitor and is licensed for the treatment of bone metastases. Clodronate and pamidronate are also licensed for this indication.

In addition, ZA has been demonstrated to exhibit antitumour effect. Direct and indirect mechanisms of anti-tumour effect have been postulated and at many times proven. Evidence exists that ZA antitumour effect is mediated through inhibition of tumour cells proliferation, induction of apoptosis, synergistic/additive to inhibitory effect of cytotoxic agents, inhibition of angiogenesis, decrease tumour cells adhesion to bone, decrease tumour cells invasion and migration, disorganization of cell cytoskeleton and activation of specific cellular antitumour immune response. There is also clinical evidence from clinical trials that ZA improved long term survival outcome in cancer patients with and without bone metastases. In this review we highlight the preclinical and clinical studies investigating the antitumour effect of bisphosphonates with particular reference to ZA.

1. Introduction

Bisphosphonates are proven to be effective in preventing/delaying skeletal-related events in patients with bone metastases and potentially preserving functional independence and quality of life. This effect is mediated by the inhibitory effect of bisphosphonates on osteoclasts.

Recently, it has been reported that bisphosphonates may have anti-tumour effect as well.

There are two classes of bisphosphonates that differ with regard to structure and mechanism of action [1]. The first one includes pyrophosphate-resembling bisphosphonates, such as clodronate and etidronate, which are metabolically incorporated into nonhydrolyzable adenospine tri-phosphate (ATP) analogues that act as inhibitors of ATP-dependent enzymes. The second class which is more recent and potent includes nitrogen-containing bisphosphonates (N-BPs), such as alendronate, pamidronate, risedronate, ibandronate and zoledronic acid (ZA).

N-BPs inhibit a key enzyme, farnesyl diphosphonate (FPP) synthase, in the biosynthetic mevalonate pathway. As a result, these compounds interfere with a variety of cellular functions essential for the bone-resorbing activity and survival of osteoclasts. Several intermediates in this pathway (Fig. 1), including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are required for the post-translational modification (i.e., prenylation) of guanosine triphosphate-binding proteins such as Ras, Rho, and Rac. These signalling molecules are involved in the regulation of cell proliferation, cell survival, and cytoskeletal organization [2,3].

ZA is reported to be more potent inhibitor of farnesyl diphosphate synthase than the other bisphosphonates risedronate, ibandronate, incadronate, alendronate, and pamidronate [4].

Preclinical findings provide insight into possible mechanisms of action of bisphosphonates that may explain their ability to inhibit tumour cells. This report reviews the preclinical and clinical data investigating the anti-tumour effects of ZA.

1.1. Preclinical rationale for potential anticancer effects of ZA

Preclinical data indicate that possible anti-cancer mechanisms of ZA (and other bisphosphonates) may include (Fig. 2):

- Inhibition of tumour cell proliferation and induction of apoptosis.
- Augmentation of inhibitory effect of cytotoxic agents (additive and synergistic effect).
- Inhibition of angiogenesis.
- Decrease in tumour cell adhesion to bone.
- Decrease in tumour cells invasion and migration and disorganization of cell cytoskeleton.

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http://dx.doi.org/10.1016/j.jbo.2013.12.001

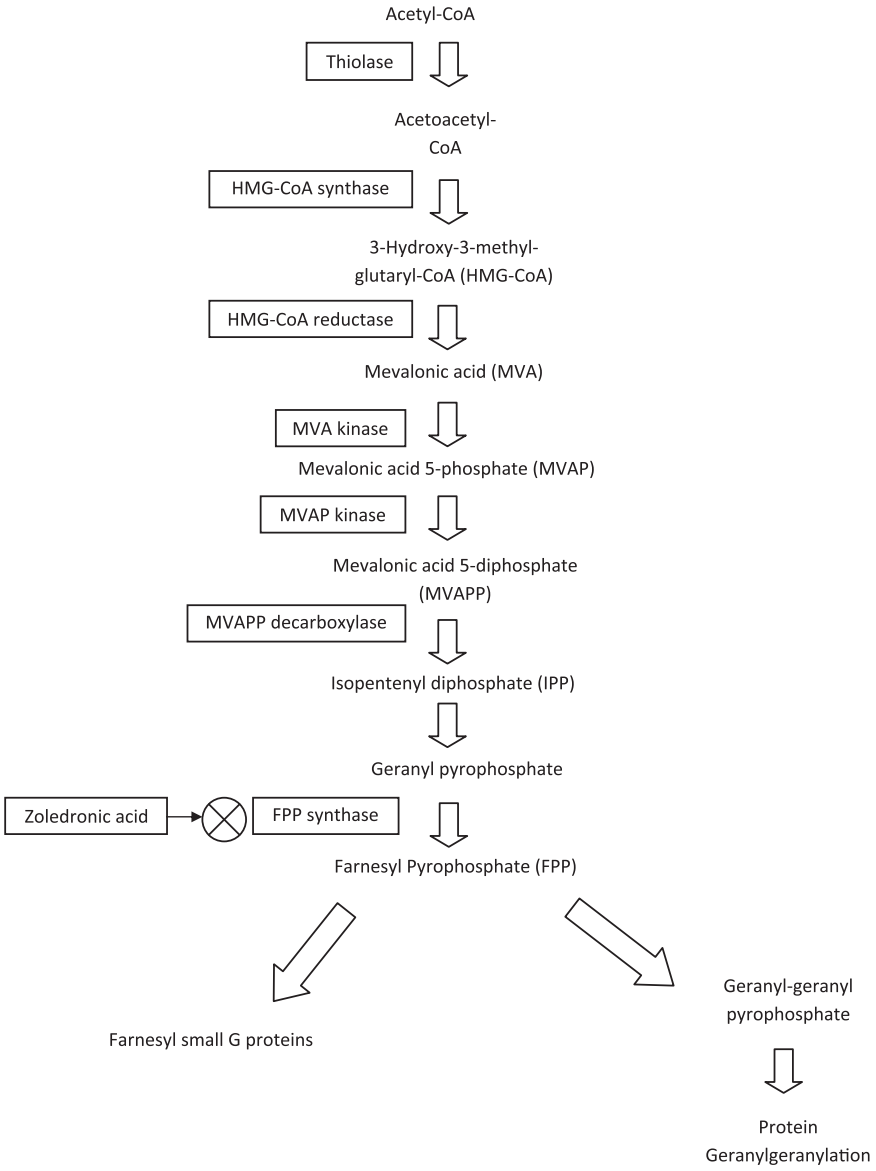

Fig. 1. Flowchart showing the mevalonate pathway.

- Activation of γδ T cells.
- Effects on tumour macrophage infiltration.

Preclinical studies investigating these possible mechanisms of action are presented below and summarized in Table 1.

1.1.1. Inhibition of tumour cell proliferation and induction of apoptosis

ZA inhibits a key enzyme of the mevalonate pathway, farnesyl diphosphonate synthase.

Inhibition of this enzyme prohibits formation of isoprenoids, such as farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP), which are required for regular prenylation of small GTPbinding proteins, like Rho and Ras (Fig. 1) [5].

There is significant preclinical evidence to support the direct antitumour effect of ZA. In a preclinical study, ZA strongly inhibited in vitro proliferation, arrested cell cycle between S and G2/M phases, and induced the apoptosis of human fibrosarcoma cells [6]. The same group of investigators reported inhibition of growth of osteosarcoma cells at the primary and secondary sites in a murine model [7].

In another study, Zwolak et al. showed that ZA can be released from bone cement (formed with increasing concentrations of ZA, up to 1 mg/1.5 cm^3 of bone cement) and the proliferation assay showed ZA to have significant dose dependent cytotoxicity in cultures of stromal giant cell tumour, multiple myeloma, and renal cell carcinoma cells [8]. In a separate study, ZA showed direct antitumor effects against four oral carcinoma cell lines at concentrations ranging from 10 to 100 μM. ZA activated the potent pro-apoptotic pathways caspase-3, -8 and -9 and induced cellular apoptosis and increased the number of cells in apoptosis. Western blot analysis showed that ZA increased cleaved anti-human poly(ADP-ribose) polymerase expression and decreased Bcl-2 and Bid expression [9]. In renal cancer cell lines (ACHN, A-498 and CAKI-2), a significant reduction in viable cells was seen for all three cell lines following treatment with ZA (at concentrations of 6.25–100 μM), compared with untreated controls. A concomitant increase in the apoptosis significant caspase-dependent M30 antigen was demonstrated. This effect could be blocked by the pan-caspase inhibitor Z-VAD [10]. Similar apoptotic effect of ZA (in concentrations of 5–40 μM)