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Bisphosphonates for cancer treatment: Mechanisms of action and lessons from clinical trials

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ABSTRACT

A growing body of evidence points toward an important anti-cancer effect of bisphosphonates, a group of inexpensive, safe, potent, and long-term stable pharmacologicals that are widely used as osteoporosis drugs. To date, they are already used in the prevention of complications of bone metastases. Because the bisphosphonates can also reduce mortality in among other multiple myeloma, breast, and prostate cancer patients, they are now thoroughly studied in oncology. In particular, the more potent nitrogen-containing bisphosphonates have the potential to improve prognosis. The first part of this review will elaborate on the direct and indirect anti-tumoral effects of bisphosphonates, including induction of tumor cell apoptosis, inhibition of tumor cell adhesion and invasion, anti-angiogenesis, synergism with anti-neoplastic drugs, and enhancement of immune surveillance (e.g., through activation of γδ T cells and targeting macrophages). In the second part, we shed light on the current clinical position of bisphosphonates in the treatment of hematological and solid malignancies, as well as on ongoing and completed clinical trials investigating the therapeutic effect of bisphosphonates in cancer. Based on these recent data, the role of bisphosphonates is expected to further expand in the near future outside the field of osteoporosis and to open up new avenues in the treatment of malignancies.

Contents

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ATP, adenosine triphosphate; FPP, farnesyl pyrophosphate; HER, human epidermal growth factor receptor (EGFR); IL, interleukin; IPP, isopentenyl pyrophosphate; i.v, intravenous; MM, multiple myeloma; TAM, tumor-associated macrophage; VEGF, vascular endothelial growth factor.

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1. Introduction

Bisphosphonates (also called diphosphonates) are inhibitors of osteoclastic bone resorption and are therefore used in the treatment of a variety of skeletal disorders such as Paget's disease of the bone, osteoporosis (including postmenopausal and glucocorticoid-induced forms), and heritable skeletal disorders in children (for example, osteogenesis imperfecta). Additionally, bisphosphonates are used in the management of (tumor-induced) hypercalcemia and to reduce skeletal-related events resulting from bone involvement in hematological or solid malignancies. Since the first clinical trial to assess the effectiveness of the bisphosphonate clodronate in suppressing the excessive mobilization of skeletal calcium in patients with multiple myeloma (MM) (Siris et al., 1980), various clinical trials have followed across a range of malignancies. In the first part of this review, we will discuss the rationale to use bisphosphonates in cancer patients. In the second part, we will review the current clinical position of bisphosphonates in the treatment of hematological and solid malignancies.

2. Mechanisms of action

Structurally, the bisphosphonates are synthetic analogues of the naturally occurring pyrophosphates of the bone matrix. The bisphosphonates can be further divided into 2 subclasses based on their structure and molecular mechanism of action: (i) the simple and (ii) the nitrogen-containing bisphosphonates (Widler et al., 2012). The first group consists of the following clinically available molecules: clodronate, etidronate, and tiludronate. Alendronate, ibandronate, pamidronate, risedronate, and zoledronate are examples of bisphosphonates that belong to the second category (Fig. 1). Two routes of administration are used for treatment with bisphosphonates, intravenously (i.v.) and per os. Under ideal conditions, less than 1% of an orally administered dose is absorbed due to the negative charge hampering transport across the lipophilic cell membrane. Bisphosphonates exhibit a short plasma half-life, are not metabolized, and are excreted unchanged by the kidneys. Roughly 50% of the absorbed dose will bind to bone, mostly avidly at sites of active remodeling (Watts & Diab, 2010). For example, when the standard clinical dose of 4 mg zoledronate i.v. is being administered, a plasma half-life of 105 min and a peak plasma concentration (CMax) of 1–2 μM are recorded (Kimmel, 2007).

2.1. Effect on bone density

The primary pharmacological action of the bisphosphonates involves the inhibition of osteoclastic bone resorption. The simple bisphosphonates are metabolized by osteoclasts into methylene-containing analogues of adenosine triphosphate (ATP), resulting in a deficiency of usable ATP and induction of osteoclast apoptosis (Coxon et al., 2006). The nitrogen-containing bisphosphonates, which are more potent inhibitors of bone resorption, act primarily by inhibiting farnesyl pyrophosphate (FPP) synthase, a key enzyme of the mevalonate pathway. This results in a depletion of the isoprenoid lipid FPP and of geranylgeranyl diphosphate in the osteoclast, which, in turn, causes osteoclast dysfunction and reduced bone resorption (Coxon et al., 2006). Within the context of cancer, this may indirectly reduce the development and progression of bone metastases as well as the overall skeletal tumor burden.

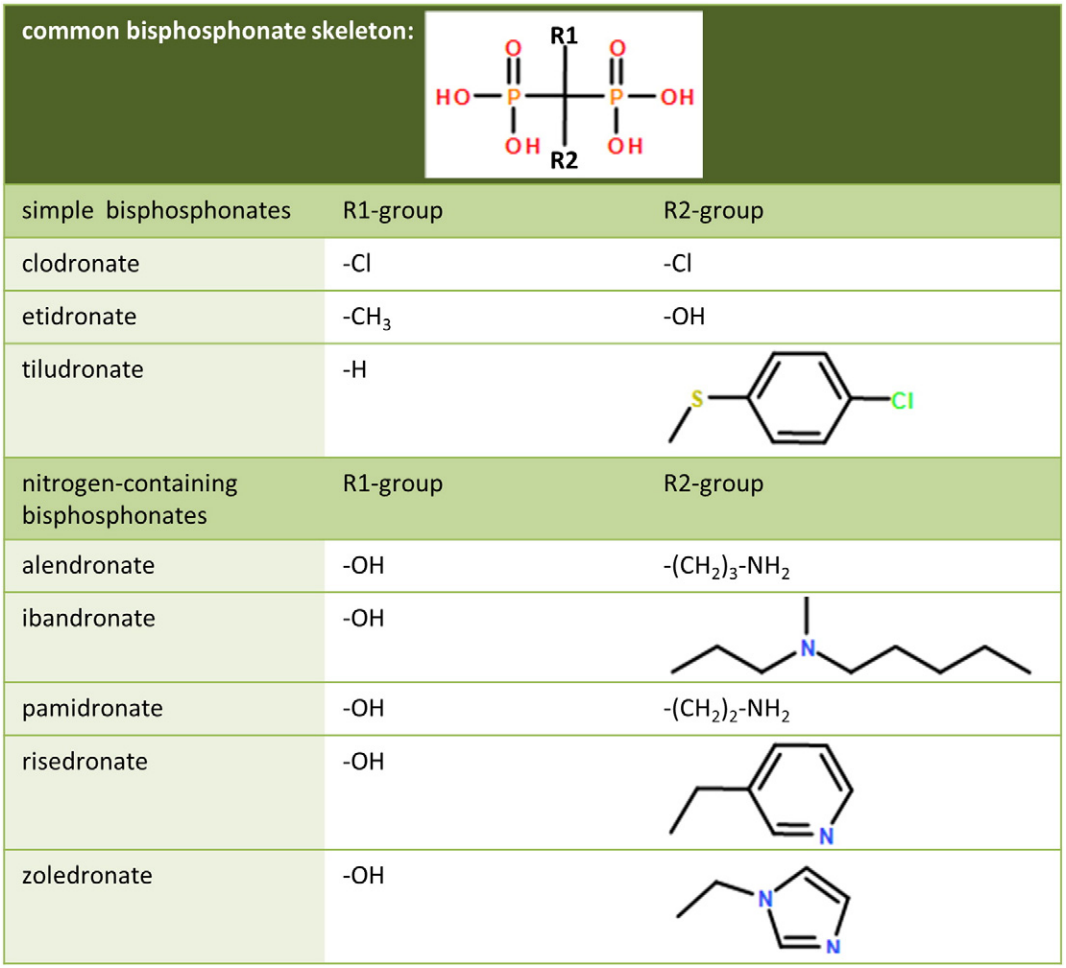

Fig. 1. Chemical structure of the bisphosphonates.