Bisphosphonates as Adjuvant Therapy for Breast Cancer

Michael Gnart, MD, Peter Dubsky, MD, Florian Fitzal, MD, Thomas Bachleitner-Hofmann, MD, Ruth Exner, MD, Peter Blaha, MD, Raimund Jakesz, MD, Walter Schippinger, MD, and Richard Greil, MD

Introduction
Breast cancer is the most common malignancy among women worldwide. Emerging results from clinical trials in patients with breast cancer suggest that, in addition to preventing cancer treatment–induced bone loss, bisphosphonates may improve disease-free survival (DFS). Although the first adjuvant studies using the early generation oral bisphosphonate clodronate suggested potential reductions in distant recurrence versus placebo in patients with early breast cancer, subsequent results with clodronate were inconsistent, and oral pamidronate produced no disease recurrence benefits versus chemotherapy alone in this setting. In contrast, addition of the newer bisphosphonate zoledronic acid to adjuvant therapy reduced disease recurrence rates and improved DFS compared with adjuvant endocrine therapy alone in two phase 3 studies in postmenopausal women with early breast cancer. Adjuvant zoledronic acid also significantly improved DFS compared with endocrine therapy alone in premenopausal women with breast cancer. Data from ongoing and future trials will further define the role of bisphosphonates in the adjuvant breast cancer setting.

Preclinical and Early Clinical Evidence for Antitumor Activity of Bisphosphonates
In addition to their protective effects on bone tissue, BPs have been shown to both directly and indirectly affect cancer cells in vitro and in animal model systems, and these properties could produce clinically meaningful antitumor effects [7••]. There is a strong preclinical rationale for the antitumor activity of BPs, and early clinical data are providing further insight into the mechanisms of action of this important class of compounds.

Direct antitumor effects
Preclinical studies have suggested that BPs may inhibit tumor progression and metastasis by affecting multiple key
steps in the metastatic process (Fig. 1) [8]. The first step of metastasis, tumor cell invasion, is initiated when angiogenesis in the primary tumor allows the cancer cells to invade the bloodstream, wherein it forms multicelled aggregates that lodge in capillary beds. Once in the capillary beds, cancer cells can extravasate from the blood vessels and develop into secondary tumors in the bone or visceral organs. Emerging research suggests that cancer cells in the bone marrow can also lay dormant for an extended time before developing into bone lesions or mobilizing to cause disease recurrence in other distant sites [9].

In vitro studies demonstrated that BP treatment can induce apoptosis and inhibit migration, adhesion, and invasion by human cancer cell lines [7••]. In preclinical and model systems, zoledronic acid has been shown to reduce tumor-associated angiogenesis [7••]. Additionally, in pilot clinical trials, both pamidronate (single infusion of 90 mg) and zoledronic acid (four weekly infusions of 1 mg) were shown to reduce circulating levels of vascular endothelial growth factor (VEGF) in patients with metastatic bone disease [10,11].

Some BPs have also been shown to have single-agent antitumor effects and to synergize with the cytotoxic or cytostatic effects of chemotherapy agents (Table 1) [7••, 12–23]. For example, concomitant exposure to either ibandronate or zoledronic acid enhanced the cytostatic effects of cyclophosphamide/methotrexate/5-fluorouracil and epirubicin in combination with cyclophosphamide or docetaxel on human primary breast cancer cells [15]. In a murine model of human breast cancer, zoledronic acid alone and zoledronic acid plus doxycycline reduced bone tumor burden by 43% and 74%, respectively, compared with untreated mice [22]. Sequential exposure to cytotoxic agents followed by zoledronic acid appears to potentiate the antitumor effects. For example, exposure to doxorubicin (2 mg/kg) followed 24 hours later by zoledronic acid (100 μg/kg) synergistically decreased intraosseous tumor burden in bone and increased rates of cancer cell apoptosis compared with either treatment alone or both treatments administered simultaneously [23].

Indirect antitumor effects
During remodeling and repair of bone, osteoclast-mediated osteolysis releases growth factors from the bone matrix, which can promote the growth of cancer cells into tumors [8]. Indeed, cell lines derived from human breast