

# Optimizing Bisphosphonate Therapy in Oncology

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Over the last 20 years, bisphosphonates have been investigated for the treatment of bone metastases and have been shown to reduce the associated skeletal complications. Intravenous administration of bisphosphonates is generally safe and well tolerated with long-term use, and the development of more potent, second- and third-generation bisphosphonates has greatly improved the convenience (due to shorter infusion time) and clinical activity of these agents. Traditionally, bisphosphonates have been used to prevent skeletal complications in patients with breast cancer and multiple myeloma and to treat hypercalcemia of malignancy. Zoledronic acid (Zometa®; Novartis Pharmaceuticals Corp.; East Hanover, NJ) is a new-generation bisphosphonate that has demonstrated the broadest clinical activity of all the available bisphosphonates. Recent evidence suggests that bisphosphonates also have direct antitumor effects at clinically achievable concentrations, suggesting that the future role of bisphosphonates may continue to expand. This supplement summarizes the proceedings of the symposium titled "Optimizing Bisphosphonate Therapy in Oncology" held in Davos, Switzerland, on March 26, 2004. It provides an overview of the clinical benefit of bisphosphonates in the treatment of cancer. Specifically, the articles contained in this supplement describe preclinical and clinical findings, aspects of safety and compliance, and the future of bisphosphonate therapy.

Advances in this field have come from the introduction of new-generation bisphosphonates. In his review, *Dr. Coleman* discusses how a number of bisphosphonates, including zoledronic acid, reduce the incidence of skeletal complications in patients with breast cancer and indicates that zoledronic acid has demonstrated broad clinical activity in patients with a wide variety of tumor types including prostate cancer, lung cancer, and renal cell carcinoma. In addition to the

clinical benefits of bisphosphonate therapy, *Dr. Coleman* discusses the various end points used in clinical trials of bisphosphonates and their relative merits [1].

Safety and compliance are other timely topics discussed by *Dr. Conte et al.* [2]. He points out that i.v. bisphosphonates require only monthly dosing and are well tolerated over the long term in patients with bone metastases. The risk of decreased renal function is similar to that from placebo when i.v. bisphosphonates are administered at the recommended doses and infusion times. In contrast, oral bisphosphonates are associated with gastrointestinal toxicities that can lead to early discontinuation or noncompliance, which can reduce clinical efficacy. Additionally, i.v. administration of bisphosphonates appears to be more effective in patients with hypercalcemia of malignancy and for the prevention of skeletal complications.

*Dr. Green* reviews the preclinical evidence that zoledronic acid has antitumor activity against a variety of tumor types and discusses the molecular mechanisms underlying this activity [3]. In particular, zoledronic acid has been shown to disrupt the interactions between tumor cells and the bone microenvironment that promote tumor growth in the bone. He further describes the evidence that zoledronic acid significantly inhibits the growth of both osteolytic and osteoblastic tumors in animal models. Interestingly, zoledronic acid can also inhibit the formation of bone metastases in androgen-deficient mice. These preclinical findings have important clinical implications regarding the potential inhibition of cancer-treatment-induced bone loss (CTIBL), as *Dr. Lipton* points out in a subsequent section, and are the motivation for continued clinical research in this area [4].

Finally, *Dr. Lipton* discusses the future of bisphosphonate therapy [4]. Importantly, bisphosphonates appear promising

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for the prevention of CTIBL in patients with breast or prostate cancer who are receiving estrogen- or androgen-ablative hormonal therapies. Moreover, bisphosphonates have demonstrated antitumor activity in preclinical models, including effects on tumor growth in soft tissues, and clinical evidence suggests that bisphosphonates may slow the progression of

bone lesions or prevent bone metastasis. Therefore, trials are ongoing to determine the clinical antitumor effects of zoledronic acid in patients with early-stage breast cancer, prostate cancer, non-small cell lung cancer, and renal cell carcinoma. Based on the results of these trials, the role of bisphosphonates in the oncology setting is likely to further expand.

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## REFERENCES

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