

# Effective Salvage Treatment of Recurrent Ewing Sarcoma Utilizing Chemotherapy and Zoledronic Acid

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## Introduction

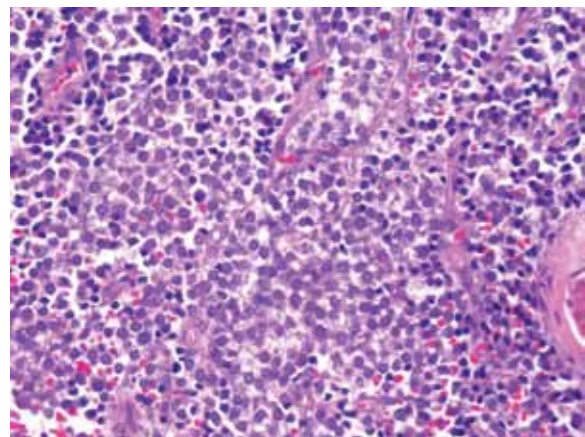
We would like to report a case of recurrent Ewing sarcoma treated with chemotherapy and zoledronic acid (Zometa, Novartis), resulting in an impressive clinical and positron emission tomography (PET) scan response. As there are no data regarding the use of bisphosphonates in Ewing sarcoma, this report may be useful in furthering clinical management. Zoledronic acid has been widely used in a variety of settings for many years and has an excellent safety profile. Indeed, one may wonder why bisphosphonates have not previously been evaluated in metastatic Ewing sarcoma and other primary malignancies of bone where the prognosis of recurrent disease, regardless of therapy, is often poor.

## Case Report

A 33-year-old white man presented with an 8.3 × 5.6 cm mass of the right scapula in December 2005. This was biopsied, and the pathology was consistent with Ewing sarcoma. The tumor was composed of sheets of monotonous small, round, blue cells that were positive for CD99 and negative for CD3, CD20, epithelial membrane antigen (EMA), terminal deoxynucleotidyl transferase (TdT), and S-100 protein by immunohistochemistry, supporting the diagnosis of Ewing sarcoma (Figure 1). Flow cytometric evaluation of the tumor excluded the possibility of a hematolymphoid neoplasm. Fluorescent in situ hybridization was performed on air-dried touch preparations of the tumor utilizing a dual color break-apart probe positioned at the Ewing sarcoma breakpoint

locus, localized to 22q12. Separation of the dual colors confirmed a rearrangement of chromosome 22 and a diagnosis of Ewing sarcoma. Imaging studies consisted of computed tomography (CT) scans of the chest, abdomen, and pelvis, which were negative, and a bone scan, which was positive at the right scapula. A bone marrow examination was negative for tumor cells.

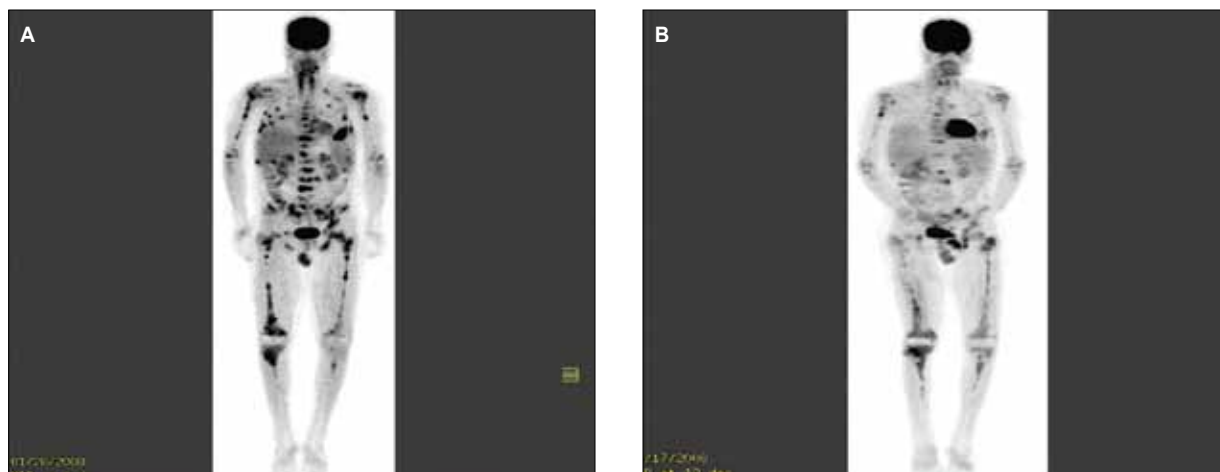
The patient was started on ifosfamide and etoposide chemotherapy alternating with vincristine, adriamycin, and cytoxan.<sup>1</sup> Between January 30, 2006 and March 3, 2006, he received concurrent radiation to the scapula for a total dose of 52.4 Gy at 1.2 Gy twice per day. By January 2007, he had finished his adjuvant chemotherapy, but within 2 months, he began to develop shoulder pain. At this time, pretreatment imaging with a PET/CT scan using 18F-fluorodeoxyglucose (FDG) showed areas of abnormal uptake in the lumbar, thoracic, and



**Figure 1.** High-power photomicrograph of the tumor, which was composed of sheets of monotonous small round cells separated by thin fibrovascular septa (hematoxylin and eosin stain, original magnification × 400).

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**Figure 2.** Positron emission tomography scan before (A) and after (B) treatment.

cervical spine, right anterior ribs, left iliac bone, and also some air space disease consistent with a recent infection (Figure 2A). Magnetic resonance imaging (MRI) of the spine showed multiple lesions involving C5, T12, and L5. The C5 lesion extended to the central canal and the neural foramina. The patient required increasing pain medications and underwent palliative radiation to the C spine, right hip, and right pelvis.

He then received cyclophosphamide and topotecan chemotherapy for 6 cycles until September 21, 2007.<sup>2</sup> Unfortunately, after a period of temporary improvement, there was progression of disease on a repeat PET/CT scan. The patient continued to require intensive pain control medications. He was switched to gemcitabine and docetaxel, but by December 2007 progression of disease once again necessitated a change of his chemotherapy regimen.

At this time, he was started on intravenous irinotecan and temozolomide using a 21-day cycle.<sup>3</sup> After a thorough discussion with the patient, intravenous zoledronic acid at a standard dose of 4 mg every 4 weeks was added to his regimen. This was done in the hope of ameliorating his bone pain and preventing pathologic fractures. Following 6 cycles of chemotherapy and 4 monthly injections of zoledronic acid, a PET/CT scan using 18F-FDG showed marked improvement in all sites of disease (Figure 2B). In addition, the patient's pain level decreased significantly and he experienced no side effects or adverse events that could be attributed to zoledronic acid.

## Discussion

Ewing sarcoma is a rare tumor in adults.<sup>4</sup> Treatment of localized Ewing sarcoma with a combination of chemotherapy, surgery, and/or radiation therapy results in a

5-year survival of approximately 65%.<sup>1,5</sup> Recently, dose-intensive chemotherapy has improved these results. Unfortunately, however, when metastatic disease occurs or when metastases are present at the time of initial diagnosis, a survival of only 25% can be expected at 5 years.<sup>5-8</sup>

Staging patients with Ewing sarcoma (as we did) is, as expected, a work in progress. Arguments are being made for increasing the use of FDG-PET scanning in pediatric sarcomas in general.<sup>9-11</sup> Pediatric principles are employed in managing adult patients suffering from Ewing sarcoma. In a recent study of 46 children with sarcomas, of whom 23 had Ewing sarcoma, Volker and colleagues evaluated the impact of conventional imaging studies (CIM; CT scanning, ultrasound, MRI, and bone scanning) with side-by-side analysis of FDG-PET imaging. They concluded that the 2 types of imaging complemented each other. PET-FDG was superior in demonstrating lymph node and bone metastases, whereas CT scanning was more reliable in demonstrating lung lesions. In Ewing sarcoma, FDG-PET was superior to bone scanning at 88%, versus 37% for conventional imaging, as defined above. In osteogenic sarcoma, however, the sensitivities were similar for CIM versus the FDG-PET scan.<sup>10</sup> Similar results were also reported in a retrospective study that noted a greater sensitivity of Ewing sarcoma bone lesions, which were detected by the FDG-PET scan at 88%, versus 69% for a bone scan. In osteosarcomas, bone scanning was superior.<sup>12</sup> It is postulated that the permeative and destructive nature of Ewing sarcoma in the bone makes FDG-PET more sensitive in contrast to the well-known osteoid formation in osteosarcomas, which makes bone scanning very relevant in such pathophysiology.<sup>12</sup> The superiority of FDG-PET compared to the bone scan was also supported in a report by Gyorke and coworkers in patients with Ewing sarcoma and primitive neuroec-

dermal tumors, the latter of which are biologically very similar to Ewing sarcoma.<sup>13</sup> The use of FDG-PET scans may also be useful in the ongoing management of and response to treatment in Ewing sarcoma.<sup>14,15</sup> In our case, the demonstration of bony lesions by FDG-PET was quite dramatic and consistent with a tumor response when repeated.

Although the Ewing family of tumors may be extraskeletal, bone involvement as a primary site and as a metastatic site is typical. In many malignancies that involve the bone, such as breast, prostate, lung, other solid tumors, and multiple myeloma, the use of bisphosphonates with chemotherapy is a common recommended clinical practice. Tumors treated with bisphosphonates thus usually involve the bone both in hematologic and nonhematologic diseases with therapeutic effect.<sup>16-19</sup> Nonskeletal beneficial effects are also being increasingly recognized. In a recent large study from Austria, women with primary breast cancer were randomized to hormonal therapy alone versus zoledronic acid every 6 months for 3 years. Patients given zoledronic acid did much better than those on hormonal therapy, raising the probability of efficacy beyond the bone environment.<sup>20</sup> Thus, it is interesting that bisphosphonates, which have been around for a long time, have been overlooked in treating primary tumors of bone such as Ewing or osteogenic sarcomas. It may be that these 2 tumors largely occur in the younger age group where bisphosphonates such as zoledronic acid are otherwise rarely used.

The effectiveness of bisphosphonates and their basic mechanisms of action continue to be elucidated. These include anti-angiogenesis mechanisms<sup>21-24</sup> and a multiplicity of other anticancer effects alone or in combination with chemotherapy and/or biologic agents.<sup>20,25-29</sup>

Bisphosphonates modulate many aspects of skeletal physiology, and it is postulated that this group of agents may have additional incompletely understood anti-tumor effects. Some of these effects include inhibition of tumor cell growth, altered adhesion of tumor cells, reduced invasive capacity, and enhanced apoptosis.<sup>30-33</sup> Sonnemann and associates suggested the possibility of using bisphosphonates in Ewing sarcomas based on the benefits observed in a Ewing sarcoma cell line.<sup>34</sup> Zhou and coauthors studied the effects of zoledronic acid in rat models of sarcoma in which the authors used paclitaxel alone, zoledronic acid alone, and both in combination. The combination was most effective in reducing the tumor burden to a level of approximately 22% of the original, which was twice that with zoledronic acid alone.<sup>35</sup> These investigators also demonstrated that there was upregulation of osteoprotegerin, which causes apoptosis. It was suggested that zoledronic acid would be useful in the treatment of Ewing sarcoma.

The effects of zoledronic acid in osteosarcoma cell lines include increased apoptosis, reduced cell prolif-

eration and cell migration (anokis), S- phase arrest, and activation of multiple pathways such as ATM/CDK1/CDC-25.<sup>33,36-44</sup> Indeed, many more effects including inhibition of cyclins E and D1 have been demonstrated. In animal models, zoledronic acid has suppressed bone and lung metastasis.<sup>45</sup> These studies provide preliminary validation of the concept of using bisphosphonates in primary neoplasms of bone.

This case was notable for the impressive response elicited in multiply relapsed disease by the use of zoledronic acid administered together with temozolomide and irinotecan.

We believe that further study of the synergistic effects of chemotherapy and bisphosphonates, such as zoledronic acid, in neoplasms of the bone are indicated. Although various evolving paradigms have recently suggested that chemotherapy with newer agents including bisphosphonates makes sense,<sup>46</sup> we could not find a published report of a patient treated with chemotherapy and bisphosphonates in Ewing sarcoma. We hope that this case report will act as a catalyst to accelerate interest in studying bisphosphonates in Ewing sarcoma.

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# Review

## Ewing Sarcoma Treatment: A Role for Bisphosphonates?

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### Introduction

Significant basic science and clinical research advances during the last 4 decades have dramatically improved the likelihood of cure (nearing 70%) among patients diagnosed with localized tumors in the Ewing sarcoma (EWS) family. Despite this progress, the survival rate for those who have confirmed metastatic disease at diagnosis or who eventually develop relapses unfortunately remains less than 30%. This disparity in survival rates undeniably calls for improved therapeutic options but also raises questions about why our current therapies so often fail to result in cure. A plausible answer may be that current therapies are narrowly targeted at the tumors themselves, leaving the growth-conducive stromal environment and host factors largely intact.<sup>1,2</sup> To explore a novel stroma-targeted strategy for treating EWS, Siddiqui and colleagues<sup>3</sup> treated a EWS patient with the bisphosphonate zoledronic acid (Zometa, Novartis), and they noted a clinical response. Although this result was provocative, the direct effect of zoledronic acid cannot be ascertained since temozolomide and irinotecan were administered concurrently. Thus, further study is warranted.

### Current Treatment Options in Ewing Sarcoma

Although rare in the general population, EWS is the second most common bone tumor in adolescents and young adults. Treatment of EWS typically employs at least 6 cycles of neoadjuvant chemotherapy, followed by defini-

tive local control. Surgery is preferred; however, radiation therapy is used instead when complete local control through surgery is unachievable without significant risk of morbidity. After surgery or radiation therapy, patients are given another 8 cycles of adjuvant chemotherapy that can vary depending on whether a pathologic response was observed.

The addition of ifosfamide and etoposide to the backbone of vincristine, dactinomycin, doxorubicin, and cyclophosphamide (VADC)-based chemotherapies improved event-free survival for patients with localized, but not metastatic disease and therefore represents the current standard of care for frontline therapy for EWS.<sup>4</sup> Further, existing trials are attempting to maximize the chemotherapy dose per cycle, increase the total number of cycles provided, and decrease the interval between cycles (“dose-dense therapy”). When diagnosed in adulthood, patients are often treated using “pediatric” protocols using similar chemotherapies, but fare worse irrespective of the clinical setting.

As described above, the cure rate is substantially less for those with metastatic disease or recurrence, but survival is nevertheless usually markedly prolonged by treatment. Topotecan/cyclophosphamide, temozolomide/irinotecan,<sup>5-7</sup> and high-dose ifosfamide have proven benefits and are internationally accepted as second-line salvage therapies.<sup>1,6</sup> Since many patients with metastatic or recurrent EWS will have received extensive prior treatment, a particular advantage of the temozolomide/irinotecan regimen is that it is relatively nonmyelosuppressive and can be conveniently administered in the outpatient setting. Agents biologically targeted against specific proteins, such as insulin-like growth factor-1 receptor or mammalian target of rapamycin, are showing promise among a subset of patients with refractory EWS and remain at the forefront of experimental therapies.

### Does Zoledronic Acid Benefit Patients with EWS?

With an improved understanding of the “seed and soil” hypothesis prominently advocated by Stephen Paget,<sup>8</sup> one naturally questions whether the osteoid matrix and surrounding stroma serve to promote the growth of EWS, a tumor type that, though not of osteoblast derivation, most often originates within the associated marrow mesenchymal stem cells. When used in fighting other cancer types such as breast, prostate, or lung cancer that have a tendency for bony metastases, bisphosphonates (particularly nitrogen-containing third-generation ones like zoledronic acid) have been demonstrated to reduce the incidence of skeletal metastasis by as much as 40%—presumably by affecting the “soil” through direct

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inhibition of osteoclast-mediated bone resorption, which, in simplest terms, reduces potential space for invading malignant cells.<sup>9</sup> Though one might expect this activity to be most useful for controlling extraskeletal tumors, one of the first indications for which zoledronic acid was approved by the US Food and Drug Administration was for treatment of multiple myeloma, which, like EWS, is by and large marrow derived (10% of EWSs are extraskeletal). Though these 2 diseases clearly have very different behavior and etiology, that shared similarity could at least offer a biologic rationale for testing zoledronic acid purely based on its direct bone-related effect.

As Siddiqui and colleagues highlight, beyond the indirect theoretical effect altered bone turnover may have upon EWS, zoledronic acid and other nitrogen-containing bisphosphonates appear to have intrinsic anti-neoplastic effects as well. In vitro experiments conducted by Sonnemann and associates<sup>10</sup> showed an 80% reduction in EWS cell viability with pamidronate at 50 mM. Zhou and coworkers<sup>11</sup> observed a similar effect using 30 mM zoledronic acid and extended this observation to an orthotopic preclinical mouse model in which antitumor effects were thought to be secondary to upregulated osteoprotegerin, and subsequent apoptosis.

While these results offer preliminary evidence supporting the use of third-generation bisphosphonates in patients with EWS as part of a clinical trial, it should be noted that the preclinical concentrations used to achieve substantial in vitro cell kill were at least 30 times as high as the maximum human serum concentrations known to occur after the monthly administration of 4 mg zoledronic acid over 15 minutes. Since zoledronic acid accumulates at up to a 1,000-fold higher concentration within bone, the lower clinical dose may not be a limiting factor at that site. However, such meager concentrations in the serum or lung would be of obvious clinical importance since the vast majority of EWS-related deaths are attributable to widespread pulmonary metastases. Instances of jaw osteonecrosis have been reported to occur in cancer patients receiving zoledronic acid, and known side effects such as renal insufficiency could be problematic, since as standard of care, most EWS patients will have received nephrotoxic agents such as ifosfamide, which have long-lasting subclinical residual effects. Additionally, though reported anecdotally, the use of bisphosphonates in very young children remains controversial.<sup>12,13</sup>

## Conclusion

Given the evidence presented above, it is tempting to surmise that zoledronic acid had a beneficial chemotherapeutic effect in the patient reported by Siddiqui and colleagues. However, since temozolomide and irinotecan were administered with the bisphosphonate, the anticipated clinical response obfuscates whatever role, if any, zoledronic acid played. The Euro-Ewing 2008 study (ClinicalTrials.gov identifier NCT00987636), which provides adjuvant zoledronic acid or placebo to a low-risk subset of EWS patients (those with localized EWS and good histologic response or with initial tumor volume <200 mL), should prove enlightening. Until zoledronic acid is further studied in a randomized controlled clinical trial, its routine integration into EWS management cannot be advocated.

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