

A pilot study of zoledronic acid in the treatment of patients with advanced malignant pleural mesothelioma

Muhammad Omer Jamil
Mary S Jerome
Deborah Miley
Katri S Selander
Francisco Robert

Division of Hematology and
Oncology, Department of Medicine,
Comprehensive Cancer Center,
University of Alabama at Birmingham,
Birmingham, AL, USA

Purpose: Malignant pleural mesothelioma (MPM) is a rare malignancy with a dismal median survival of <12 months with current therapy. Single and combination chemotherapy regimens have shown only modest clinical benefit. In preclinical studies, nitrogen-containing bisphosphonates (zoledronic acid) inhibit growth of mesothelioma cells by different mechanisms: inhibition of mevalonate pathway, inhibition of angiogenesis, activation of apoptosis through caspase activation, and alteration in activity of matrix metalloproteinases, thereby affecting invasiveness of cancer cells.

Patients and methods: We investigated the role of zoledronic acid in a pilot, single-arm trial of MPM patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2 who had progressed on prior treatments or had not received systemic therapy due to poor PS. Primary end point was composite response rate by modified response evaluation criteria in solid tumors and/or metabolic response by 2-deoxy-2-[fluorine-18]fluoro-D-glucose (¹⁸F-FDG) positron emission tomography criteria. Secondary end points were progression-free survival (PFS) and overall survival (OS). Exploratory end points include the effect of zoledronic acid therapy on vascular endothelial growth factor (VEGF), basic fibroblast growth factor, interleukin 8, transforming growth factor beta, mesothelin, and osteopontin levels.

Results: Eight male patients (median age of 62 years) with the following clinical characteristics were treated; ECOG PS was 0–2, 75% with epithelioid type, and 62% had prior chemotherapy. Overall composite response rate was 12.5% and the clinical benefit rate (response + stable disease) was 37.5%. Median PFS was 2 months (0.5–21 months) and median OS was 7 months (0.8–28 months). No treatment-related toxicities were observed. Lower VEGF levels were predictive of favorable response and mesothelin levels correlated with disease course.

Conclusion: Zoledronic acid shows modest clinical activity without significant toxicity in patients with advanced MPM.

Keywords: mesothelioma, treatment, bisphosphonates

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumor of serosal surfaces. Its incidence is increasing worldwide due to asbestos use.¹ MPM occurs mainly in men, aged 60–80 years, and the majority of them die due to local extension and/or respiratory failure.^{1,2} Median survival of patients ranges from 12 to 19 months with combination chemotherapy. Pemetrexed plus cisplatin, the current standard chemotherapy regimen, yield a median overall survival (OS) of 12.1 months and a median time to progression of 5.7 months.³ Poor prognostic markers include: poor performance status (PS), high

Correspondence: Francisco Robert
Division of Hematology and Oncology,
Department of Medicine, Comprehensive
Cancer Center, University of Alabama at
Birmingham, 1824 Sixth Ave South, WTI
210B, Birmingham, AL 35294-3300, USA
Tel +1 205 934 5077
Fax +1 205 975 7428
Email pacorobertuab@cs.com

leukocyte count, high platelet count ($>400,000/\mu\text{L}$), nonepithelial tumor type, and male gender.⁴ Despite new chemotherapy combinations, MPM patient outcome is modest,^{5–11} thus a great need for improvement exists.

Bisphosphonates are osteoporosis drugs that have been in clinical use for decades.¹² In addition to their antiresorptive effects in osteoporosis and cancer-induced osteolytic bone disease, nitrogen-containing bisphosphonates (such as zoledronic acid and risedronic acid) inhibit tumor proliferation.^{12–14} Zoledronic acid effectively inhibits proliferation of mesothelioma cell lines in vitro and in vivo.¹⁵ This result is likely an outcome of mevalonate pathway inhibition,^{12,16} leading to depletion of prenyl groups needed in posttranslational modification and activation of small GTPases,¹⁴ ultimately inhibiting cell growth. In addition, zoledronic acid reduces experimental malignant pleural effusions.¹⁷ It demonstrates antiangiogenic effects^{18–20} and suppresses vascular endothelial growth factor (VEGF) blood levels.²¹ VEGF levels have been associated with MPM progression and poor survival^{22,23} in relation to high tumor microvessel density.^{22,24}

Computed tomography (CT) response evaluation criteria in solid tumors (RECIST) is difficult to use in MPM due to circumferential and axial growth. Thus, MPM response to treatment is usually measured with imaging using modified RECIST assessment criteria.²⁵ MPM is 2-deoxy-2-[fluorine-18]fluoro-D-glucose (¹⁸F-FDG) positron emission tomography (PET) avid,²⁶ and ¹⁸F-FDG PET scans can be used to document early responses^{27,28} and have been useful in the assessment of prognosis and staging.^{29,30} Mesothelin and osteopontin are glycoproteins that are overexpressed in mesothelioma and are associated with tumor progression. Serum markers such as mesothelin and osteopontin are of interest for prognosis, tumor response, and tumor progression.^{31–33} On the basis of these findings, we conducted a pilot, proof-of-concept feasibility study of zoledronic acid in the treatment of advanced MPM. We measured the levels of antiangiogenic factors (VEGF, bFGF, IL-8, and TGF- β), mesothelin, and osteopontin before and during treatment.

Patients and methods

Study design and patients

This single-arm, prospective study was conducted at the University of Alabama at Birmingham Comprehensive Cancer Center. The primary objective of this study was to evaluate the antitumor activity of zoledronic acid in subjects with unresectable, advanced MPM assessed by the modified RECIST criteria,²⁵ and/or metabolic response ¹⁸F-FDG PET assessment.³⁴ The secondary objectives were to assess duration of

response, progression-free survival (PFS), OS, and safety and tolerability of zoledronic acid in MPM patients. Blood levels of VEGF, bFGF, IL-8, TGF- β , mesothelin, and osteopontin were measured to investigate the influence of zoledronic acid.

Inclusion criteria included: adult patients (age >18) with unresectable MPM who had progressed after one or more prior systemic therapies, had not received prior systemic therapy due to poor PS, and/or were unwilling to receive systemic chemotherapy. Other eligibility criteria included life expectancy of at least 2 months, measurable disease by CT or ¹⁸F-FDG PET, willing to consent to contraception (if applicable), and ability to provide consent. Exclusion criteria were brain metastasis, second cancer diagnosis, heart disease (class 3 or 4 heart failure by New York Heart failure classification), acute coronary syndrome (within 6 months), known human immunodeficiency virus or hepatitis, clinically significant arrhythmias, serious acute systemic disease, dental disease, and history of osteonecrosis of the jaw.

This study was approved by the Institutional Review Board at the University of Alabama at Birmingham Comprehensive Cancer Center. Written informed consent was obtained from all study participants.

The study was registered with the National Clinical Trials Network, number NCT01204203.

Treatment and assessments

Study schema is presented in Figure 1. Patients were treated with intravenous (IV) infusion of zoledronic acid (Novartis Pharmaceuticals, East Hanover, NJ, USA) 4 mg IV over 15 minutes on day 1 of a 3-week cycle. Patients were evaluated for response every 2 cycles with CT scans and ¹⁸F-FDG PET scans only on cycle 2. Subjects with either stable disease or response continued treatment until disease progression and/or intolerable toxicity at which patients were taken off study. Dose adjustment was allowed per standard guidelines for zoledronic acid for decreased creatinine clearance. Subjects were monitored for toxicity using National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 criteria. Patients who completed at least one treatment cycle were included in data analysis.

Sample collection and analysis for correlative objectives

Blood samples for VEGF, bFGF, IL-8, TGF- β , mesothelin, and osteopontin were collected prior to treatment on days 1 and 8 of cycle 1 and then prior to treatment on day 1 of cycles 2, 3, and 6. Plasma samples were aliquoted and stored at

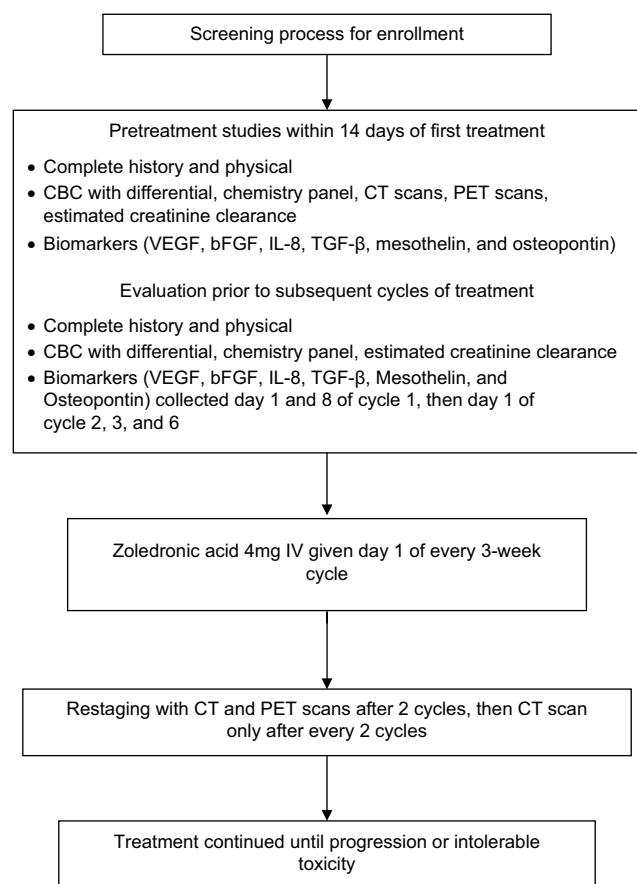


Figure 1 Study schema.

Abbreviations: bFGF, basic fibroblast growth factor; CBC, complete blood count; CT, computed tomography; IL-8, interleukin 8; IV, intravenous; PET, positron emission tomography; TGF- β , transforming growth factor beta; VEGF, vascular endothelial growth factor.

–70°C. Blood levels of these biomarkers were analyzed using ELISA (enzyme-linked immunosorbent assay) kits from R&D systems (R&D Systems, Inc., Minneapolis, MN, USA) Quantikine assays, according to manufacturer's instructions.

Statistical analysis

Responses were assessed as composite response rate which include modified RECIST objective responses and metabolic response ^{18}F -FDG PET assessment. Data are presented as descriptive statistics. OS and PFS are presented as median, whereas VEGF, bFGF, IL-8, TGF- β , mesothelin, and osteopontin are presented as mean values.

Results

Demographics

From November 2010 to January 2015, 9 patients consented, but only 8 patients were treated. All patients were male (7 Caucasian and 1 African-American), median age of 62 years (age range 49–77), and Eastern Cooperative Oncology Group (ECOG) PS 0–2. Three patients were never-smokers. One patient had stage 2 disease, and 7 patients had stage 4 disease. The majority of the patients (n=6) had epithelioid mesothelioma. All except 2 patients reported a history of asbestos exposure. All patients included in this study had symptomatic, active disease with measurable parameters by CT and PET scans; previously treated patients had progressive symptomatic disease after the last line of treatment. Three patients were treatment naïve, whereas others had received one or more lines of chemotherapy agents, including pemetrexed/cisplatin or carboplatin, single-agent carboplatin, pemetrexed, and cediranib.

Treatment outcomes

Median duration of follow-up was 1.3 months (0.3–21 months), median number of treatment cycles was 2 (1–28 cycles). Baseline tumor parameters and response assessment after cycle 2 of treatment are summarized in Table 1. No response was seen when patients were evaluated by modified RECIST

Table 1 Summary of baseline tumor parameters and response assessment after cycle 2 of treatment

Patient no.	Baseline parameters		Restaging after cycle 2		Overall assessment of response
	CT ^a (cm)	^{18}F -FDG PET ^b	CT ^a	^{18}F -FDG PET ^b	
1	13.5	12.9	14.6 cm (8% \uparrow)	8.8 (32% \downarrow)	Stable disease
2	19.4	49.0	24 cm	New FDG lesions	Progressive disease
3	4.7	13.8	3.0 cm	6.2 (44% \downarrow)	Stable disease
4	4.0	52.0	New lesion and \uparrow pleural effusion	43.6	Progressive disease
5	14.5	44.5	–	–	Rapid global deterioration after cycle 1
6	9.8	12.2	15.0 cm	12.9 Increased size and max SUV of nontarget lesions	Progressive disease
7	37.6	78.9	–	–	Progressive disease; rapid global deterioration after cycle 1
8	12.0	45.13	19.5 cm	54.0	Progressive disease

Notes: ^aSum of the unidimensional measurement of measurable parameters. ^bSum of max SUVs of tumor parameters.

Abbreviations: CT, computerized tomography; ^{18}F -FDG, 2-deoxy-2-[fluorine-18]fluoro-d-glucose; PET, positron emission tomography; SUV, standardized uptake value.

criteria; 2 patients had the best response of stable disease, 1 response lasted 21 months. When assessed with ^{18}F -FDG PET, 1 patient with stable disease by modified RECIST had partial response by ^{18}F -FDG PET criteria, whereas another patient thought to have progressive disease by modified RECIST had stable disease by ^{18}F -FDG PET criteria. Overall composite response rate was 12.5%. Clinical benefit rate (response + stable disease) was 37.5%. Median PFS was 2 months (0.5–21 months). Median OS was 7 months (0.8–28 months). The histopathological characteristics of the MPM responders include 1 epithelioid and 1 mixed histology; all 6 MPM nonresponders had epithelioid histology. No treatment-related toxicities were observed.

Correlative studies result

Higher baseline levels of VEGF and osteopontin were observed in nonresponders (Table 2). Decreasing levels of mesothelin and osteopontin were seen in patients with response or stable disease. Zoledronic acid initially led to increase in VEGF levels in all patients with subsequent decrease. Increasing VEGF levels was seen in patients with progressive disease. No association with disease burden or progression was seen with IL-8, bFGF, or TGF- β .

Discussion

This pilot feasibility study assessed whether bisphosphonates could have a role in the treatment of mesothelioma due to their antiangiogenic properties. Our findings suggest that zoledronic acid has single-agent activity in MPM treatment. Angiogenesis is a complex process, difficult to target due to multiple VEGF-dependent and VEGF-independent pathways.^{35,36} Multiple antiangiogenic agents have been previously used for the treatment of MPM; however,

responses have been modest with bevacizumab having the most evidence.^{37–47} A recent publication reporting the combination of bevacizumab with pemetrexed and cisplatin showed increased PFS and OS.⁴¹ Zoledronic acid can mitigate angiogenesis at subcellular level by mevalonate pathway inhibition and is beneficial in antitumor therapy.^{14,15,48–50} In our study, clinical benefit in at least 2 patients was observed without toxicity, which makes this drug an attractive agent for combination with chemotherapy or other antiangiogenic agents for future trials. Lower VEGF levels were associated with favorable responses similar to previous results.^{41,42,51} However, an interesting finding was the initial increase and then decrease in VEGF levels with zoledronic therapy in responder patients (Table 2). It has been shown that maximal tolerated chemotherapy increases the expression of VEGF and other proangiogenic growth factors in a rebound response to treatment. It is possible that similar initial rebound effect can be seen with zoledronic acid in responders; and more profound effect in nonresponders, indicative of an adaptive (evasive) mechanism of resistance.⁵²

IL-8 and bFGF, which have been shown to enhance neovascularization and promote tumor growth,⁵³ did not correlate with zoledronic acid therapy. Serum mesothelin levels are elevated in MPM, but is not used as a biomarker for diagnosis due to low sensitivity.^{31,54,55} It has been shown to correlate with prognosis^{56–58} and has been a target for MPM immunotherapy.^{59,60} Our study reports that mesothelin and osteopontin levels decline in patients who have favorable therapy response and potentially may represent promising biomarkers of this disease.

In our patient population, as well as in the SEER Cancer Statistics, the incidence of mesothelioma is much more common in men than in women.⁶¹ This prevalence is reflected in the demographic data of our study. Previous studies have shown women diagnosed with mesothelioma typically have more favorable outcomes and a statistically better chance of survival than males.⁶¹

Table 2 Correlative analysis of VEGF, mesothelin, and osteopontin blood levels during treatment with zoledronic acid

Biomarker	Type of response	Mean baseline values	Mean level after first or second zoledronic acid treatment	Mean level at last sample collection
VEGF ^a (pg/mL)	Responders	48.7	58.5	42.9
	Nonresponders	190.6	260.98	265.7
Mesothelin ^b (ng/mL)	Responders	84.4	70.4	38.9
	Nonresponders	56.4	70.8	82.7
Osteopontin ^c (ng/mL)	Responders	11.6	0	34.95
	Nonresponders	20.7	24.9	24.9

Notes: ^aNormal range =31–86 pg/mL. ^bNormal range =9.6–40.6 ng/mL. ^cNormal range =0.3–20 ng/mL.

Abbreviation: VEGF, vascular endothelial growth factor.

Conclusion

Our pilot study suggests modest activity of zoledronic acid as a single agent in the treatment of mesothelioma and warrants further investigation in combination with other agents.

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Disclosure

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