Phase II Study of Dasatinib in Patients with Previously Treated Malignant Mesothelioma (Cancer and Leukemia Group B 30601)

A Brief Report

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Introduction: We conducted a phase II trial of dasatinib in malignant mesothelioma (MM) patients to evaluate its toxicity and efficacy as a second-line treatment.

Methods: Patients with unresectable MM and no symptomatic effusions were given dasatinib 70 mg twice daily as part of a 28-day cycle. We also measured plasma vascular endothelial growth factor and platelet-derived growth factor β and colony stimulating factor 1 (CSF-1) and mesothelin-related protein at baseline and during therapy.

Results: Forty-six patients were enrolled in this study. Fifty percent of the first 12 patients enrolled experienced ≥grade 3 treatment-related adverse events, and therefore, the starting dose was reduced to 50 mg twice daily. Grade 3 and 4 toxicities included fatigue (11%) and pleural effusion (9%). The overall disease control rate was 32.6%, and progression-free survival at 24 weeks was 23% (95% confidence interval: 13.5–40.0%). Survival was markedly longer in patients with lower pretreatment CSF-1 levels and in patients whose CSF-1 levels decreased from baseline during therapy.

Discussion: Single-agent dasatinib has no activity in MM and is associated with pulmonary toxicities that prohibit its use in an unselected MM population.

Key Words: Dasatinib, Mesothelioma, SRC kinase.

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Cisplatin in combination with pemetrexed is now a standard first-line treatment for malignant mesothelioma (MM).[1] However, once patients fail treatment with a pemetrexed-containing regimen, there is no standard of care available. Dasatinib, an aminothiazole analog, is an orally administered protein tyrosine kinase inhibitor with activity against several dysfunctional signaling pathways in MM, including the SRC family kinases, vascular endothelial growth factor (VEGF), platelet-derived growth factor β (PDGFβ) receptor, and several other protein tyrosine kinases.[2,3] This study was based on the hypothesis that dasatinib would have direct and indirect antiproliferative effects on mesothelioma and would slow disease progression no longer controlled with first-line platinum and pemetrexed therapy. As secondary endpoints, we analyzed the effect of dasatinib on plasma VEGF and PDGF levels. In addition, we followed levels of serum CSF-1 because it activates mitogen-activated protein kinase in myeloid progenitors through an SRC-dependent mechanism[4] and serum mesothelin-related protein because it is known to be decreased in patients responding to mesothelioma therapy.[5]

PATIENTS AND METHODS

Patient Selection

Eligible patients were >18 years of age, had histologically confirmed MM not amenable to curative surgery, had unidimensionally measurable disease, and an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients were excluded if they were pregnant, nursing, on antithrombotic or antiplatelet agents, or had documented brain metastases, symptomatic pleural effusion, or serious cardiac disease, or bleeding disorders. Patients were required to fail one and only one pemetrexed-containing chemotherapy regimen. Patients were allowed to have received prior intrapleural therapy with sclerosing agents or bleomycin. At least 4 weeks were required since prior major surgery and 4 weeks since first-line chemotherapy or radiotherapy to lesions other than those used for measurement. Patients were required to have adequate hematologic, hepatic, and renal function and an electrocardiogram showing a QTc interval of <450 milliseconds.

All patients provided informed consent before receiving study treatment, and the study was approved by the Institutional Review Boards of participating institutions.

Treatment Schedule

Dasatinib was given orally at an initial fixed dose of 70 mg twice daily. After 23 patients had enrolled, however, the dose was reduced to 50 mg twice daily because of poor tolerance, including fatigue and pleural effusion. One cycle was defined as 28 days.

Study Endpoints and Analysis

The primary objective of this study was to determine the rate of progression-free survival (PFS) at 24 weeks. Secondary objectives included description of (1) response rate (complete response [CR] + partial response [PR]); (2) response duration; (3) overall survival (OS); (4) toxicity; and (5) analysis of plasma VEGF and PDGF and serum CSF-1 and mesothelin-related protein levels. Response assessment was performed using modified RECIST criteria as described before.[6] A computed tomography scan was performed at baseline and every 8 weeks until the patient had documented progression. Plasma VEGF was analyzed using Human VEGF Quantikine ELISA kit (R&D Systems, Minneapolis, MN), and plasma PDGF was analyzed using Human PDGF-AB ELISA kit (Insight Genomics, Falls Church, VA). Serum CSF-1 levels were detected using Human M-CSF Immunoassay Quantikine kit (R&D Systems, Minneapolis, MN), and serum mesothelin-1-related protein levels were analyzed using MESOMARK assay (Fujirebio Diagnostics, Inc, Malvern, PA).

Sample Size Considerations

Sample size was determined as before[7] by applying the following considerations: if the true 24-week PFS rate for the single agent was ≥54%, we would conclude that the agent was worthy of further investigation. However, if the true 24-week PFS rate was ≤34%, we would conclude that the agent was not worthy of further investigation. Under constant hazards, a 24-week PFS of 34 and 54% corresponded to a median PFS of 3.55 months and 6.22 months or a hazard ratio (HR) of 1.75. Forty-three eligible patients were to be enrolled in the study. The probability of erroneously concluding that the treatment was worthy of further investigation ($p \geq 0.54$) when the success rate was truly ≤34% ($p \leq 0.34$) was 0.06. The probability of erroneously concluding that the treatment was not worthy of further investigation ($p \leq 0.34$) when the success rate was truly ≥54% ($p \geq 0.54$) was 0.13. If 19 or fewer (42.9%) eligible patients were successful in their treatment, we would conclude that the treatment was not worthy of additional investigation.

Statistical Analysis

OS was measured from the day of registration until date of death; living patients were censored at the date of last follow-up. PFS was measured from the day of registration until disease progression or death, whichever came first; living patients who did not progress were censored at the date of last follow-up. Progression was defined as at least a 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions. Kaplan-Meier estimates were used to illustrate PFS and OS curves. The correlation of response rate and biomarkers was examined using Wilcoxon rank sum test. In multivariate analysis, a logistic regression model was used to explore the relationship of response rate and biomarkers after adjusting for other significant prognostic factors. To examine the relationship between these biomarkers and PFS and OS, a log-rank test and a Cox's proportional hazard model was used, after adjusting for other prognostic factors.

RESULTS

Drug Safety

Forty-six patients were enrolled in this study from September 15, 2007, to August 31, 2009, (Table 1). Three patients withdrew from the study before treatment initiation, leaving 43 patients eligible for evaluation. Six of the first 12 patients experienced grade ≥3 adverse events. After 23 patients had enrolled in the study, the starting dose of dasatinib was decreased from 70 to 50 mg twice daily. The most common grade 3 and 4 nonhematologic events were fatigue (11%), pleural effusion (9%), and dyspnea (7.5%). One patient developed grade 3 pericardial effusion. The most common grade 3 or 4 hematologic events (7% of patients) were grade 3 anemia (2%) and lymphopenia (4%). A greater percentage

TABLE 1. Baseline Characteristics

Variable	$n = 46^a$
Age	
Median, yr (range)	68 (35–81)
Gender	
Male	31 (72%)
Female	12 (28%)
ECOG performance status	
0	19 (44%)
1	24 (56%)
Site of origin	
Pleura	36 (84.0%)
Peritoneum	6 (14.0%)
Other	1 (2.0%)
Histology	
Epithelial	33 (77%)
Biphasic	5 (12%)
Sarcomatoid	2 (5%)
Missing	3 (7%)
Prior therapy	
Chemotherapy	43 (100%)
Radiation	6 (14.0%)
Surgery	23 (53%)

[a]Three patients were excluded because they withdrew from study before starting therapy.

ECOG, Eastern Cooperative Oncology Group; *N*, number of patients.

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