Phase 2 Study of Sorafenib in Malignant Mesothelioma Previously Treated with Platinum-Containing Chemotherapy

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Introduction: The incidence of mesothelioma is rising. First-line cisplatin and pemetrexed confers a survival benefit, with a median progression-free survival (PFS) of 5.7 months. Sorafenib inhibits tyrosine kinases, including receptors for vascular endothelial growth factor, which are implicated in mesothelioma pathogenesis by preclinical and clinical data.

Methods: Sorafenib, at 400 mg twice daily, was assessed in a single-arm multicenter phase 2 study, using Simon's two-stage design. Eligible patients had received platinum combination chemotherapy earlier. The primary endpoint was PFS at 6 months, with secondary endpoints, including response rate and metabolic response, assessed using fluorodeoxyglucose positron emission tomography. Published reference values for PFS in mesothelioma provide a benchmark for the null hypothesis of 28% progression-free at 6 months, and for moderate or significant clinical activity of 35% or 43% progression-free at 6 months, respectively.

Results: Fifty-three patients (72%) were treated. Most had epithelioid histology. Ninety-three percent of patients had a performance status 0 or 1. Treatment was well tolerated with few grade 3 or 4 toxicities. Median PFS was 5.1 months, with 36% of patients being progression-free at 6 months. Nine percent of patients remained on study beyond 1 year. Changes in fluorodeoxyglucose positron emission tomography parameters did not predict clinical outcome.

Conclusions: Sorafenib is well tolerated in patients with mesothelioma after completion of platinum-containing chemotherapy. PFS of sorafenib compares favorably with that reported for other targeted agents, and suggests moderate activity in this disease.

Key Words: Mesothelioma, Sorafenib.

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Malignant mesothelioma is a disease of the mesothelial surfaces of pleural and peritoneal cavities. More than 80% of cases are pleural, and there is an overwhelming relationship with exposure to asbestos.[1] The incidence of the disease is predicted to continue to rise in the current decade.[2] Combination platinum chemotherapy with the antifolate pemetrexed has become the standard of care as first-line treatment. Median overall survival (OS) is 11.4 and 12.1 months in phase 3 trials, which combined third-generation antifolates with cisplatin.[3,4] In the second-line setting, no standard has yet been established.

A significant role for angiogenesis in the evolution of mesothelioma has been suggested, both by preclinical in vivo and cell-line studies, and by translational data from patient samples. Elevated or overexpressed vascular endothelial growth factor (VEGF), VEGF-C, fibroblast growth factor-1 and -2 (FGF-1 and FGF-2), tumor necrosis factor beta, VEGFR-1/FLT-1, kinase domain insert receptor/VEGFR-2, and VEGFR-3/FLT-4 have been associated with mesothelioma.[5–8] Local production of VEGF leads to receptor phosphorylation in an autocrine loop, which can be arrested in vitro with neutralizing antibodies to both VEGF and its receptors.[8] Antisense oligonucleotides that inhibit VEGF and VEGF-C, antibodies to VEGFR-2 and VEGFR-3, and directly conjugated VEGF-diphtheria toxin, have all been shown to inhibit mesothelioma cell growth in vitro.[9] Furthermore, there is an inverse correlation between circulating VEGF and FGF-2 and survival,[6,8,10] with higher levels of pretreatment VEGF possibly acting as a predictive marker for antiangiogenesis in mesothelioma.[11] Taken together, this evidence provides a rationale for a therapeutic disruption of angiogenesis pathways in mesothelioma.

Sorafenib was originally developed as an Raf-1 kinase inhibitor.[12] It was subsequently found to be a potent inhibitor of both wild-type B-Raf, and oncogenic B-Raf V600E

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serine/threonine kinases, and of the proangiogenic receptor tyrosine kinases VEGFR1/2/3, platelet-derived growth factor receptor-β, FGFR-1, c-Kit, FLT-3, and RET.[13] In xenograft models of human colon cancer, and murine and human renal-cell carcinoma, sorafenib significantly reduced tumor microvascular density.[13,14] Combinations of antiangiogenic effects, inhibition of signaling through the MAPK pathway, and MAPK-independent induction of apoptosis have all been shown to contribute to in vivo sorafenib activity in multiple-tumor xenograft models.[15–18] Sorafenib has undergone extensive investigation in a range of solid tumors,[19–24] and is approved for the treatment of clear-cell renal and hepatocellular carcinoma.[25,26] We conducted a phase 2 study of sorafenib in patients with mesothelioma, previously treated with first-line pemetrexed plus platinum chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients had malignant pleural mesothelioma not suitable for surgery. Relapse after surgery was allowed. All patients had received first-line chemotherapy with pemetrexed and platinum. Patients had an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2 and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria modified for mesothelioma.[27] Adequate bone marrow, renal, liver, and coagulation function, as defined by protocol-mandated laboratory tests within 7 days of starting the first dosage, were required, and patients were excluded in the presence of significant congestive cardiac failure or arrhythmias requiring antiarrhythmic therapy, or other major comorbidity such as uncontrolled hypertension, impaired immunity, active infection, coagulopathy, anticoagulation, thrombosis, or hemorrhage. Prior palliative radiotherapy was permitted. The study was approved by the U.K. national research ethics service, and all patients signed written informed consent before commencement of study procedures.

Study Treatment and Evaluation

This was a single-arm phase 2 study of continuous dosing with sorafenib 400 mg twice daily, with a cycle defined as 28 days. Dosage interruptions were permitted for toxicity, as were dose reductions (to 400 mg once daily, then to 400 mg alternate days if required) for any grade 3 or 4 toxicity (excluding hypertension, diarrhea, or rash not adequately treated with supportive medication), or for recurrent grade 2 toxicity after dosage interruption. Patients were reviewed in the clinic on days 1 and 15 of the first cycle, and on day 1 of each subsequent cycle. Safety blood tests, including thyroid function and blood pressure observations were performed regularly. Treatment was continued until disease progression, withdrawal of consent, or unacceptable toxicity.

Baseline disease was imaged by computed tomography (CT), with subsequent scans performed at 8-weekly intervals, using modified RECIST.[27] A subgroup of sequentially recruited patients underwent a baseline fluorodeoxyglucose positron emission tomography (FDG-PET) scan with low-dose CT at baseline, and at 8 weeks after commencing sorafenib.

Statistical Methods

The primary endpoint of the study was progression-free survival (PFS) at 6 months. Secondary endpoints were partial response rate assessed by CT scan, disease control rate (partial response rate plus stable disease rate), and OS. Change in FDG-PET-CT avidity was included as an exploratory endpoint. For FDG-PET, changes in maximum standardized uptake value, metabolic tumor volume, and total lesion glycolysis were assessed before and after 8 weeks of treatment.

Using published reference data for PFS at 6 months, a null hypothesis of 28%, and an alternative hypothesis of 43% were assumed.[28] Accrual of 55 patients was required for a significance level of 0.10 with an 80% power to detect whether the true 6-month PFS would be more than 43%. A two-stage optimum design was used,[29] with an initial 19 patients enrolled and evaluated for 6-month PFS, planned such that the trial would be continued only if six or more of the 19 patients were progression-free at 6 months. OS and PFS were estimated using the Kaplan–Meier method. Data were collected through an electronic database (MedSciNet AB, Stockholm, Sweden), and statistical analysis was performed using SSPS. The relationship between the changes in FDG avidity and outcome (PFS and OS) was assessed using Pearson's correlation coefficient, using SPSS version 20 with a significance level of p equal to 0.05.

RESULTS

Patients Characteristics

Fifty-six patients were recruited at three centers between November 2008 and April 2011. Three patients were excluded because of ineligibility. Baseline characteristics are shown in Table 1. Overall, 77% were men, with 72% having epithelioid histology. PS was 1 or better in the greater majority of patients (93%). In total, 225 cycles of sorafenib were administered, with a median number of four cycles.

Toxicity

All patients were evaluable for toxicity assessment, shown in Table 2. The most common grade 3/4 adverse events were fatigue (15%), palmar-plantar erythrodysesthesia (13%), and rash (9%). Other toxicities, namely diarrhea, mucositis, anorexia, alopecia, dysphonia, nausea, vomiting, constipation,

TABLE 1. Baseline Patient Characteristics

Patient Characteristics		
Age (range, yr)		66 (49–82)
Sex (%)	Men	41 (72)
	Women	12 (23)
Histology (%)	Epithelioid	38 (72)
	Sarcomatoid	2 (4)
	Mixed	8 (15)
	Not recorded	5 (9)
Performance status	0	4 (7)
	1	45 (85)
	2	4 (7)

TABLE 2. Toxicity

	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 1–4(%)
Fatigue	27 (51)	8 (15)	0	66
Rash	23 (43)	5 (9)	0	53
PPE	16 (30)	7 (13)	0	43
Diarrhea	17 (32)	1 (2)	0	34
Mucositis	16 (30)	2 (4)	0	34
Anorexia	14 (26)	4 (8)	0	34
Alopecia	12 (23)	0	0	23
Dysphonia	9 (17)	0	0	17
Nausea	7 (13)	2 (4)	0	17
Constipation	7 (13)	0	0	13
Dry skin	7 (13)	0	0	13
Puritis	6 (11)	0	0	11
Vomiting	6 (11)	0	0	11
Hypertension	4 (8)	1 (2)	0	9
Weight loss	4 (8)	1 (2)	0	9
Low mood	4 (8)	1 (2)	0	9
Chest pain	2 (4)	1 (2)	0	6
Thrombocytopenia	1 (2)	1 (2)	0	4
Back pain		1 (2)	0	2
MI		0	1 (2)	2
Knee swelling		1 (2)	0	2
Allergic reaction		1 (2)	0	2

All related or possibly related grade 3 or grade 4 adverse events are shown, together with any grade adverse events occurring at a frequency of more than 10%, for the 53 evaluable patients. Events were graded according to Common Toxicity Criteria Adverse Events version 3.

PPE, palmar-plantar erythrodysesthesia; MI, myocardial infarction.

dry skin, and pruritis, of any grade occurring in more than 10% of patients were typical for sorafenib. Only one grade 4 event was recorded—myocardial infarction in a patient previously treated for coronary artery disease. There were no deaths related clearly to the study drug. At least one dose reduction was required in 39% of patients, with a dosage interruption in 32% of patients. Twenty-one percent of patients required dose reduction in the first cycle. Eleven patients (21%) discontinued treatment because of toxicity, but most (66%) were withdrawn because of disease progression (data not shown).

Efficacy

Nineteen patients completed treatment in the first stage of the trial, with six patients being progression-free after 6 months. Therefore, recruitment of a total of 53 patients continued in the second stage. Median PFS was 5.1 months (95% CI: 3.5–6.7 months), with 36% (95% CI: 22%–49%) of patients progression-free at 6 months, and 9% of patients still receiving study drug at 1 year (Fig. 1*A*). Median OS was 9.0 months (95% CI: 6.7–11.3 months; Fig. 1*B*).

Three patients had a partial response (6%), with stable disease in 30 (56%) at 8 weeks for a disease control rate (partial response plus stable disease) of 62%. Eight patients progressed (15%) and 12 were not evaluable because of discontinuation of study drug before the first disease assessment (Fig. 2).

Functional imaging

Fourteen patients underwent paired FDG-PET-CT scans at baseline and 8 weeks, after commencing sorafenib. There was no significant correlation between any of the FDG quantitative measures and PFS or OS (data not shown).

DISCUSSION

In the evaluation of targeted agents, for which disease stabilization may be as important as response, meaningful endpoints need to be defined to ensure that only potentially active agents progress to further study. The use of PFS in single-arm trials is rational in the phase 2 study of antiangiogenic drugs in less common diseases.[30] The European Organisation for Research and Treatment of Cancer (EORTC) studied nine phase 2 trials and one phase 3 trial, involving 523 evaluable chemotherapy-naive mesothelioma patients. This group was pooled to determine PFS at 3, 4, 5, and 6 months as comparators for endpoints in subsequent studies.[28] These trials were conducted in the first-line setting but in an era before the current standard of care with platinum doublet chemotherapy was established. PFS was derived for three groups of study drug, designated as having significant, moderate, or insufficient clinical activity. Six-month PFS was determined to be 43% for an agent with significant clinical activity, and 35% for moderate activity.[28]

The primary endpoint of PFS at 6 months of 36% in this trial is indicative of moderate clinical activity for sorafenib in this disease.[28] The comparator PFS values used set a high hurdle for this second-line study because they were observed in chemotherapy-naive patients. Like other single-agent VEGFR-targeted agents in mesothelioma, the response rate was low[11,31–34] in keeping with a predominantly cytostatic role for such agents. RECIST assessment of response in this disease is less straightforward than for some other solid tumors,[27] and we explored, in a subset of patients, the utility of FDG-PET parameters as alternative predictors of outcome. None of the PET parameters (change in standardized uptake value, metabolic tumor volume, or total lesion glycolysis) correlated with PFS or OS. However, with a sample size of 14, the power to detect a correlation coefficient of r equal to 0.5 is only 46%.

Median PFS in this study was 5.1 months. A number of phase 2 trials have studied other single-agent VEGFR-targeting agents in mesothelioma. Cediranib and sunitinib showed median PFS results of 2.6 and 2.7 months, respectively, in patients pretreated with platinum.[32,35] In chemotherapy-naive patients, median PFS with vatalanib and sunitinib was 4.1 and 6.7 months, respectively.[33,35] One other trial studied sorafenib in a heterogeneous group of 50 evaluable patients, 60% of whom had been exposed to prior pemetrexed-based combination chemotherapy. The response rate was 6% with a median PFS of only 3.6 months.[31] The higher PFS seen in our trial, compared with other VEGFR inhibitors, may indicate superior activity for sorafenib than for the other drugs in this class tested in mesothelioma, but comparison with this last study[31] suggests that patient selection is likely to play a significant role. All patients treated in our trial were originally fit enough to receive platinum-based chemotherapy, all had received only one prior line of treatment, and a great majority had a PS of less than 1 on enrolment. Nevertheless, 28%

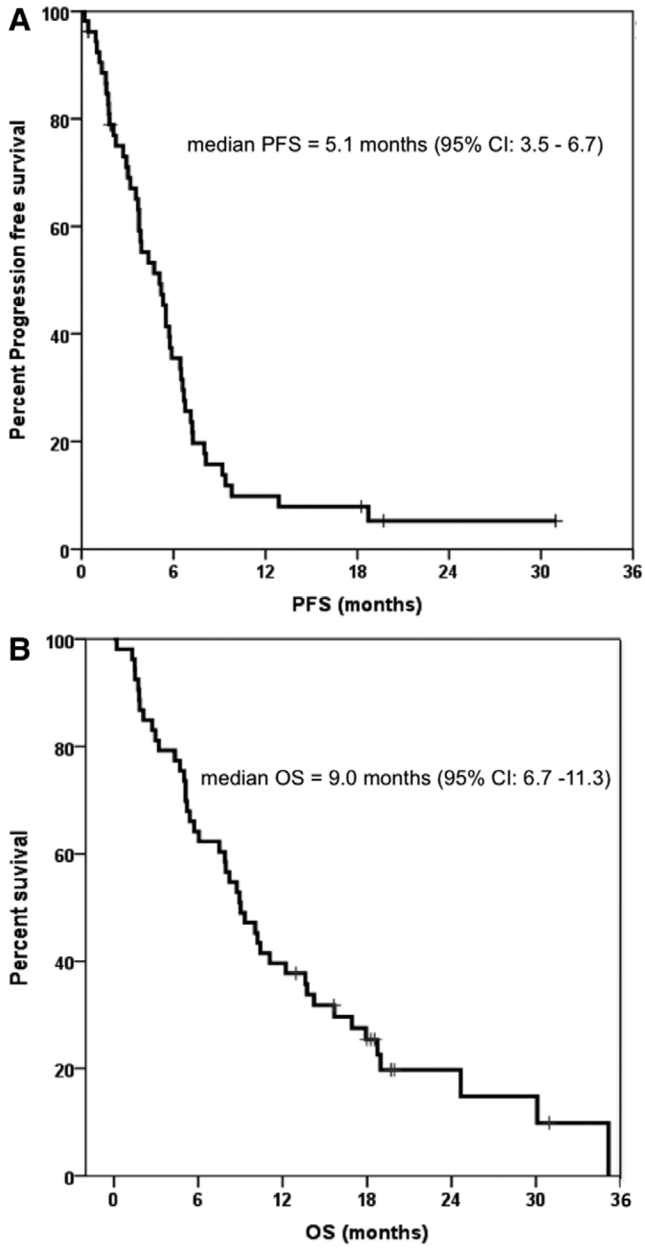

FIGURE 1. Kaplan–Meier plots for (*A*), PFS and (*B*), OS. Fifty-three patients provided data for both analyses. Median PFS was 5.1 months (95% CI: 3.5–6.7 months), with 36% (95% CI: 22%–49%) of patients progression-free at 6 months. Median OS was 9.0 months (95% CI: 6.7–11.3 months). PFS, progression-free survival; OS, overall survival; CI, confidence interval.

had nonepithelioid histology, which is associated with poor prognosis. This is a relatively high proportion compared with large published trials in this disease.[3,4]

The anti-VEGF antibody bevacizumab has been investigated in combination with gemcitabine/cisplatin chemotherapy in a placebo-controlled randomized phase 2 study. The primary endpoint was not met, but the results suggest a negative prognostic role for circulating VEGF.[11] The modest

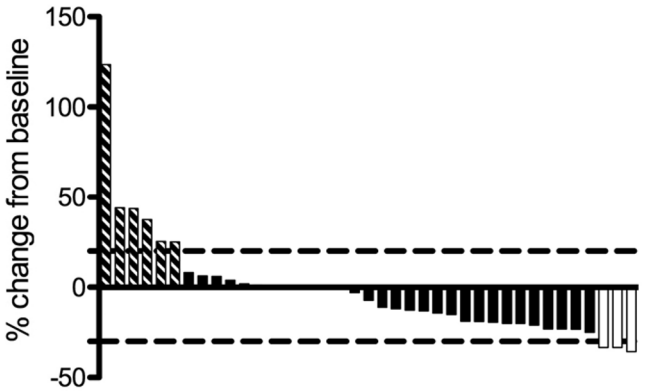

FIGURE 2. Best response by Response Evaluation Criteria in Solid Tumors criteria modified for mesothelioma. Each bar represents an individual patient. Two patients were not evaluable because of nontarget lesion progression at 8 weeks, and 12 patients did not complete the first response assessment at 8 weeks (white = partial response; black = stable disease; hatched = progressive disease).

activity of antiangiogenic drugs in this disease, despite promising preclinical rationale, may reflect the absence of any biomarker selection strategy for clinical use of these agents.

Sorafenib was well tolerated in this trial, with adequate supportive medication. The toxicity profile observed was similar to that previously reported for sorafenib. Fatigue, rash, and palmar-plantar erythrodysesthesia were common, resulting in relatively high rates of dosage interruption and reduction. However, with these interventions, and supportive medication for common toxicities, discontinuation because of intolerable toxicity occurred in only 21% of patients.

The main limitation of this study was absence of randomization.[36] This in part reflects the difficulty in defining a standard of care in this setting, although the relative rarity of the disease justifies carefully designed single-arm studies to explore activity for new treatment approaches in mesothelioma.[34] Many patients with mesothelioma remain fit even after completion of first-line chemotherapy so that placebo-controlled trials face the challenge of low patient acceptability, which can compromise recruitment.[37] However, strategies do exist to minimize placebo exposure in future trials.[38]

In conclusion, sorafenib is well tolerated in mesothelioma. It has moderate clinical activity when benchmarked against pooled historical data.[28] A median PFS of 5.1 months compares favorably with other VEGFR inhibitors in patients previously treated with first-line platinum combination chemotherapy.

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