Brief Report: A Phase II Study of Sunitinib in Malignant Pleural Mesothelioma. The NCIC Clinical Trials Group

Scott A. Laurie, MD, FRCPC, Ashish Gupta, MBBS, MD, Quincy Chu, MD, FRCPC, Christopher W. Lee, MD, FRCPC, Wojciech Morzycki, MD, FRCPC, Ronald Feld, MD, FRCPC, Alison H. Foo, MSc, Jean Seely, MD, FRCPC, John R. Goffin, MD, FRCPC, Francis Laberge, MD, FRCPC, Nevin Murray, MD, FRCPC, Sanjay Rao, MD, FRCPC, Garth Nicholas, MD, MSc, FRCPC, Janessa Laskin, MD, FRCPC, Tony Reiman, MD, FRCPC, Delia Sauciuc, MD, FRCPC, and Lesley Seymour, MD, PhD, FRCPC

Introduction: Malignant pleural mesothelioma (MPM) is an aggressive malignancy that most often presents at an advanced, incurable stage. After the failure of standard first-line cisplatin/antifolate chemotherapy, there is no accepted treatment. The vascular endothelial growth factor pathway may be a relevant therapeutic target in MPM.

Methods: This open-labeled phase II trial evaluated single-agent sunitinib, an inhibitor of multiple receptor tyrosine kinases including the vascular endothelial growth factor receptors, given at 50 mg daily orally for 4 weeks followed by a 2-week rest, in patients with advanced MPM. Two cohorts were studied: cohort 1, in which patients had previously received cisplatin-based chemotherapy, and cohort 2, consisting of previously untreated patients. A two-stage design was used for both cohorts; the primary outcome was objective response rate as determined by the RECIST criteria modified for MPM. Secondary outcomes included rates and duration of disease control, progression-free survival and overall survival, and safety and tolerability.

Results: A total of 35 eligible patients were enrolled (17 to cohort 1 and 18 to cohort 2). Neither cohort met the criteria for continuing to the second stage of accrual; only one objective response, confirmed by independent review, was observed in a previously untreated patient. Median progression-free and overall survivals were 2.8 and 8.3 months in cohort 1, and 2.7 and 6.7 months in cohort 2, respectively. Observed toxicity was within that expected for sunitinib.

Conclusions: Sunitinib, similar to other angiogenesis inhibitors, has limited activity in MPM. Future trials of angiogenesis inhibitors given as single agents in unselected patients with MPM are not warranted.

Key Words: Angiogenesis inhibitor, Mesothelioma, Systemic therapy, Phase II.

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The NCIC Clinical Trials Group, Queen's University, Kingston, Ontario, Canada.

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Address for correspondence: Scott Laurie, MD, FRCPC, the Ottawa Hospital Cancer Centre, University of Ottawa, 501 Smyth Road, Ottawa, Ontario, Canada. E-mail: slaurie@toh.on.ca

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Malignant pleural mesothelioma (MPM) is an uncommon but highly lethal cancer. After the failure of therapy with a cisplatin/antifolate combination,[1,2] there is no standard treatment.

Higher levels of vascular endothelial growth factor (VEGF) are negatively prognostic in MPM.[3] Mesothelioma cells express both VEGF ligands and receptors, suggesting an autocrine growth loop.[4,5]

Sunitinib inhibits multiple receptor tyrosine kinases, including VEGF receptors 1 to 3. Given the potential that angiogenesis inhibition might be of therapeutic benefit in MPM, the NCIC Clinical Trials Group undertook this phase II study.

METHODS

This multicenter trial had two cohorts. Cohort 1 included patients who had received ≤3 prior lines of cytotoxic chemotherapy, one of which was platinum based. Cohort 2 enrolled chemotherapy-naive patients. Patients were aged 18 years or older and Eastern Cooperative Oncology Group performance status 0 to 2, had incurable, proven MPM (any histology), and radiologically measurable disease.

This study was approved by the research ethics boards of the participating institutions. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice guidelines.

Sunitinib, provided by the Cancer Therapy Evaluation Program of the National Cancer Institute (Bethesda, MD), was administered 50 mg orally once daily for 28 days, followed by a 2-week break (1 cycle = 6 weeks), with up to two dose reductions (37.5 mg or 25 mg) for toxicity. In the absence of unacceptable toxicity or patient request, sunitinib was continued until disease progression.

Toxicity was graded using the Common Terminology Criteria for Adverse Events version 3.0 (Bethesda, MD). Response was assessed by investigators every cycle using the modification of RECIST for mesothelioma[6]; at the completion of the trial, an independent radiology review was performed.

The primary end point was objective response rate. A two-stage design[7] was used. For cohort 1, the null hypothesis was a response rate of 10% versus the alternate hypothesis of 30%, whereas for cohort 2, the values were 15% versus 35%, respectively; for both, the significance levels were $\alpha = 0.10$ and $\beta = 0.10$. For cohort 1, if ≥2 objective responses were observed in 16 patients, 10 additional patients would be accrued, and the treatment deemed of interest for further study if ≥5 responses were observed. For cohort 2, if ≥3 objective responses were observed in 17 patients, an additional 15 would be accrued, and the treatment deemed of interest if ≥8 objective responses were observed.

RESULTS

Patients

Between April 2007 and June 2009, 39 patients were enrolled (Table 1). One patient was never treated, and three were found to have no measurable disease on independent radiology review, leaving 17 eligible patients on cohort 1 and 18 on cohort 2.

TABLE 1. Patient Characteristics

Characteristics	Cohort 1 (Previously Treated)	Cohort 2 (Previously Untreated)
Eligible patients	17	18
Male	14	15
Median age (range)	65 (48–78)	70 (54–79)
ECOG performance status		
0	2	5
1	14	13
2	1	0
Number of prior cytotoxic regimens		
0	0	18
1	11	0
2	5	0
3+[a]	1	0
Histology		
Epithelioid	10	10
Sarcomatoid	1	4
Biphasic	1	1
Not otherwise specified	5	3
EORTC good prognosis class[8]	13	13

[a] One patient on cohort 1 had received a prior EGFR inhibitor.

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer.

Treatment Delivery, Toxicity, and Adverse Events

The median number of cycles of therapy in both cohorts was 3. Drug delivery was lower in the previously treated patients. Fatigue, gastrointestinal complaints, and hand-foot syndrome were the most common adverse events and the most common reasons for dose delays and interruptions. Hematological toxicity was mild, with only one grade 4 event (asymptomatic thrombocytopenia) (Tables 2–4).

Efficacy

Neither cohort proceeded to stage II. No objective responses were reported among the previously treated patients. Eleven had stable disease, for a median duration of 6 months (range: 2.3–12.7 months). The independent review confirmed these results, with a median duration of disease stabilization of 5.3 months.

One partial response (duration: 3 months) was observed among the previously untreated patients; there were 10 with stable disease for a median of 4.5 months (range: 2.5–12.7 months). The independent review confirmed the partial response and determined that 14 patients had stable disease for a median duration of 3.8 months (range: 1.1–9.0 months). Figure 1 depicts the waterfall plots for all patients.

The median progression-free survival (PFS) and overall survival (OS) for the previously untreated patients were 2.7 and 6.7 months, respectively. Median PFS and OS for the previously treated cohort were 2.8 and 8.3 months (Figures 2 and 3).

DISCUSSION

Despite preclinical evidence suggesting it may be a relevant target, angiogenesis inhibitors, for example, sorafenib,[9] have not demonstrated significant single-agent activity in MPM. In a randomized phase II trial, the addition of bevacizumab to cisplatin/gemcitabine did not improve survival.[3] Another trial of second-line sunitinib in MPM has been reported in abstract form.[10] Objective responses were observed in 10%, with a median OS of 6.7 months; the investigators felt that sunitinib had "modest" activity in this setting. In the current trial of sunitinib, only one partial response was observed, and while a majority demonstrated stable disease, this observation may simply reflect the variable natural history of MPM. The median PFS in both cohorts was less than 3 months, similar to that observed with other

TABLE 2. Drug Delivery

	Median Number of Cycles (Range)	Planned Dose Intensity	Actual Dose Intensity (Median)	% Patients Receiving >90% of Planned Dose Intensity	Patients with Dose Reduction/Off due to Toxicity
Cohort 1	3 (1–13)	233.3 mg/wk	174 mg/wk	29%	3/2[a]
Cohort 2	3 (1–9)	233.3 mg/wk	231 mg/wk	78%	9/2[b]

[a] Reasons off therapy: multiple grade 1/2 toxicities.

[b] Reasons off therapy: one each grade 4 thromboembolic event and grade 3 bronchopulmonary hemorrhage.

TABLE 3. Reported, Related Nonhematological Adverse Events Occurring At Least Once of At Least Grade 2 in Severity

	Number of Patients with NCI CTCAE (v 3.0) Grade					
	Cohort 1 (n = 17)			Cohort 2 (n = 18)		
	2	3	4	2	3	4
Cardiac general						
Hypertension	1	1		2	1	
LV systolic dysfunction	1					
Constitutional						
Fatigue	7	5		8	1	
Dermatologic						
Hand-foot	2	1				
Rash	2					
Gastrointestinal						
Anorexia	4	1		4		
Constipation	1			2		
Diarrhea	3	1		1		
Esophagitis/heartburn	1			1		
Mucositis	5			3		
Nausea	4			2		
Taste alteration	5			2		
Vomiting	2			1		
Hemorrhage						
Bronchopulmonary					1	
Epistaxis				1		
Infection						
Infection (normal ANC)	1	1				
Lymphatics						
Edema: trunk/genital		1				
Neurological						
Dizziness	1					
Pain						
Abdomen	1					
Chest		1				
Headache	1					
Muscle	2					
Vascular						
Thrombosis/embolism					1	1

Adverse events considered at least "possibly" related to sunitinib in the opinion of the investigator. Blank cells indicate no patient experienced the listed event.

LV, left ventricular.

targeted agents in both first- and second-line settings (e.g., sorafenib[9] and erlotinib[11]). By comparison, in a phase III study of pemetrexed versus best supportive care in previously

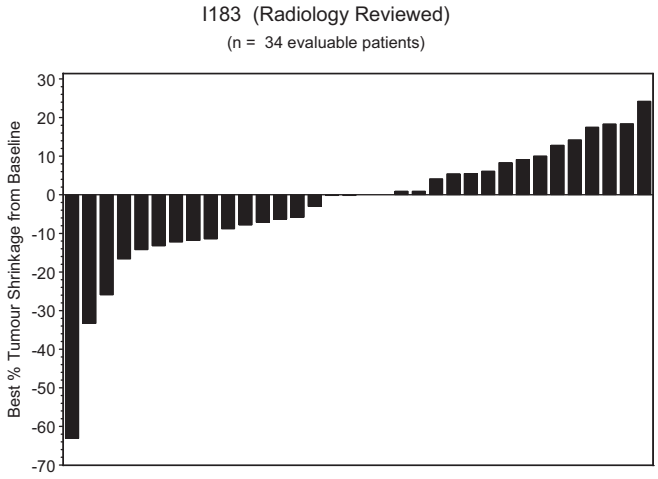

FIGURE 1. Waterfall plot of responses. Note: one patient is not included, as developed disease progression (brain metastases) and did not have target lesions reimaged.

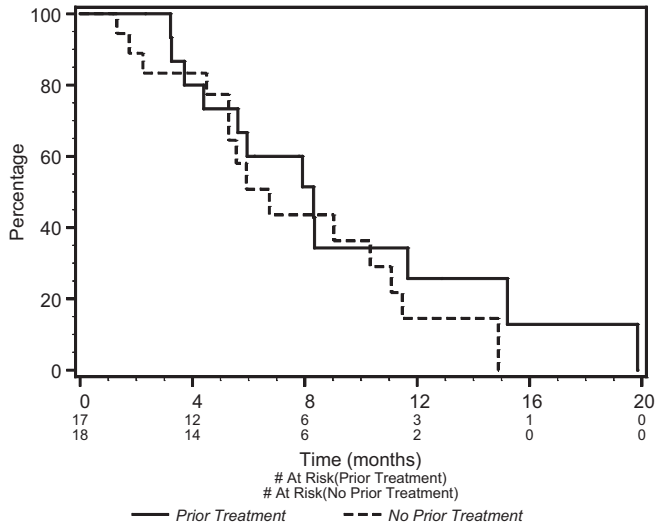

FIGURE 2. Overall survival.

TABLE 4. Hematological Toxicity

	Cohort 1 (n = 17)				Cohort 2 (n = 18)			
		Worst CTC Grade (No. of Patients)				Worst CTC Grade (No. of Patients)		
	Median Nadir (Range)	2	3	4	Median Nadir (range)	2	3	4
Leukocytes ($\times 10^9$/L)	3.8 (2.6–8.9)	3			3.7 (2.2–17.0)	5		
Granulocytes ($\times 10^9$/L)	2.2 (1.0–7.4)	3			2.25 (1.0–11.9)	4		
Hemoglobin (g/L)	103 (83–149)	8			115 (71–140)	4	1	
Platelets ($\times 10^9$/L)	195 (23–544)		1	1	212 (57–697)	1		

Toxicity graded according to NCI CTCAE version 3.0. Blank cells indicate no patient experienced the listed event.

CTCAE, Common Terminology Criteria for Adverse Events.

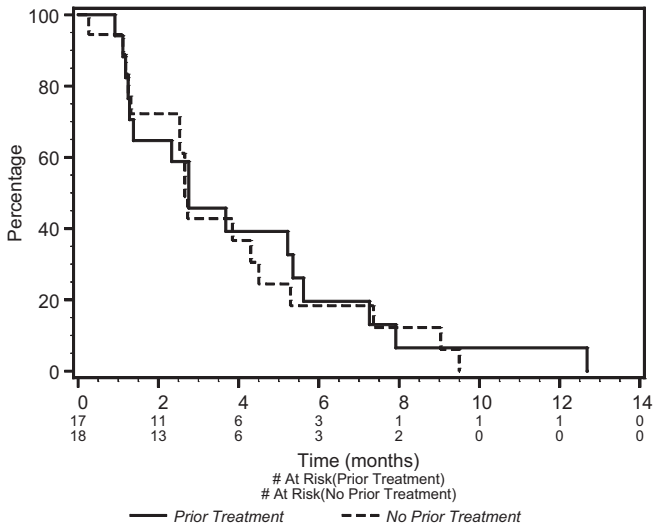

FIGURE 3. Progression-free survival.

treated MPM, pemetrexed led to objective responses in 18% and a median PFS of 3.6 months.[12]

Further study of sunitinib (or any angiogenesis inhibitor) as a single agent in unselected patients with MPM is likely not warranted. The fact that occasional dramatic objective responses have been observed suggests that there may be a subgroup that could benefit from these agents. In the randomized trial adding bevacizumab or placebo to cisplatin/gemcitabine, improved outcomes with bevacizumab were observed in patients with VEGF levels below the median value.[3] An ongoing randomized trial of cisplatin-pemetrexed with or without bevacizumab (NCT 00651456) intends to further evaluate the relationship between serum VEGF levels and outcomes.

This study had brisk accrual despite the rarity of MPM and the fact that this is generally a disease of older men who often have comorbid illnesses that could preclude enrolment to a clinical trial. The previously treated cohort, in particular, was rapidly completed, suggesting a significant unmet clinical need. This cohort had a median OS of 8 months, greater than that observed in the previously untreated cohort. Others have also observed a longer OS in previously treated patients compared with the same agent in the first-line setting,[9] but this is likely the result of patient selection rather than drug efficacy. Interestingly, in addition to the current trial, other trials of targeted agents[9,11] have reported a median OS in their previously untreated patients lower than the 12 months expected with platinum-pemetrexed.[1] Those enrolled to a clinical trial are likely suitable for standard chemotherapy, the majority of patients enrolled to both cohorts were classified as "good prognosis" by the criteria derived by the European Organization for Research and Treatment of Cancer,[8] but in this study only 3 of the 17 previously untreated patients received subsequent systemic therapy. The reasons for this are not known, and although some might have refused offered therapy, there may be a risk that exposing untreated patients to an ineffective experimental therapy impairs the subsequent delivery of standard treatment. Consideration should be given to performing studies of novel single agents in MPM only in those patients who have previously received a platinum-antifolate combination, while evaluating a new agent in conjunction with the standard chemotherapy backbone in previously untreated patients.

Determination of response in MPM may be problematic in those with only pleural rind. A modification of RECIST[6] is increasingly used in trials of MPM. The independent review performed by thoracic radiologists familiar with these criteria revealed only minor discrepancies in time to disease progression. Nevertheless, this apparent concordance between the investigators and the independent radiologists was the result of numerous data queries arising from monitoring, despite the fact that a tutorial about the modified RECIST criteria was made available to all investigators at the initiation of the trial. Others have similarly noticed the importance of educating investigators regarding the use of these criteria to ensure accurate response assessment.[13] In future trials, consideration should be given to a standardized central radiology review, particularly if response or PFS is a primary end point.

For those who have thin, nonmeasurable pleural rind as their sole disease, alternate methods of determining response are needed. Serum soluble mesothelin-related peptide may be useful in monitoring response,[14] as may fluorodeoxyglucose-positron emission tomography or positron emission tomography/computed tomography, using combinations of tumor volume and metabolic activity such as the "total glycolytic volume."[15] On-treatment changes in these measurements have been found to correlate with radiologic response and to predict survival, and total glycolytic volume values could be calculated in some patients without radiologically measurable pleural rind.[15] For response determination in these patients, either or both of metabolic imaging and soluble mesothelin levels could be combined along with subjective impression of disease change on standard computed tomography imaging.

The rarity of MPM requires the prudent conduct of trials to maximize the number of different agents, which can be studied in limited patients. There have been multiple trials of angiogenesis inhibitors, all of which have demonstrated similar, disappointing results. Greater coordination among investigators would improve efficiency and minimize the number of patients exposed to ultimately ineffective therapies.

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APPENDIX

A study coordinated by the Clinical Trials Group of the NCIC. Participating investigators were as follows:

Ottawa Hospital Cancer Centre, Ottawa, Ontario: S.A. Laurie, N.M. Reaume, and G. Nicholas.

Cross Cancer Institute, Edmonton, Alberta: Q. Chu, A.A. Joy, and A.J. Reiman.

British Columbia Cancer Agency, Vancouver, British Columbia: J.J. Laskin, B.L. Melosky, and N. Murray.

Fraser Valley Cancer Centre, Surrey, British Columbia: T. Do, K.V.J. Jasas, and C. Lee.
Cancer Centre for the Southern Interior, Kelowna, British Columbia: E. Bouttell, S.C. Rao, and D. Sauciuc.
QEII Health Sciences Centre, Halifax, Nova Scotia: W. Morzycki.
Princess Margaret Hospital, Toronto, Ontario: R. Feld.
Juravinski Cancer Centre, Hamilton, Ontario: A. Arnold and J. Goffin.
Hôpital Laval, Laval, Quebec: F. Laberge.

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