Phase II Clinical Trial of Sorafenib in Metastatic Medullary Thyroid Cancer

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ABSTRACT

Purpose

Mutations in the *RET* proto-oncogene and vascular endothelial growth factor receptor (VEGFR) activity are critical in the pathogenesis of medullary thyroid cancer (MTC). Sorafenib, a multikinase inhibitor targeting Ret and VEGFR, showed antitumor activity in preclinical studies of MTC.

Patients and Methods

In this phase II trial of sorafenib in patients with advanced MTC, the primary end point was objective response. Secondary end points included toxicity assessment and response correlation with tumor markers, functional imaging, and *RET* mutations. Using a two-stage design, 16 or 25 patients were to be enrolled onto arms A (hereditary) and B (sporadic). Patients received sorafenib 400 mg orally twice daily.

Results

Of 16 patients treated in arm B, one achieved partial response (PR; 6.3%; 95% CI, 0.2% to 30.2%), 14 had stable disease (SD; 87.5%; 95% CI, 61.7% to 99.5%), and one was nonevaluable. In a post hoc analysis of 10 arm B patients with progressive disease (PD) before study, one patient had PR of 21+ months, four patients had SD $\geq$ 15 months, four patients had SD $\leq$ 6 months, and one patient had clinical PD. Median progression-free survival was 17.9 months. Arm A was prematurely terminated because of slow accrual. Common adverse events (AEs) included diarrhea, hand-foot-skin reaction, rash, and hypertension. Although serious AEs were rare, one death was seen. Tumor markers decreased in the majority of patients, and *RET* mutations were detected in 10 of 12 sporadic MTCs analyzed.

Conclusion

Sorafenib is reasonably well tolerated, with suggestion of clinical benefit for patients with sporadic MTC. Caution should be taken because of the rare but fatal toxicity potentially associated with sorafenib.

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INTRODUCTION

Medullary thyroid carcinoma (MTC) accounts for approximately 5% of all thyroid carcinomas.¹ Most MTCs are sporadic, but approximately 20% to 30% of MTCs are associated with multiple endocrine neoplasia type 2A or 2B or familial MTC. Mutations of the rearranged during transfection (*RET*) proto-oncogene encoding for the Ret tyrosine kinase receptor have been implicated in the pathogenesis of nearly all hereditary MTCs and 30% to 50% of sporadic MTCs.² Calcitonin, secreted predominantly by parafollicular cells of the thyroid, has been widely used to assess response to therapy and to detect recurrent disease.³ Carcinoembryonic antigen (CEA) is another useful tumor marker in the management

of MTC, especially in the progressive metastatic setting when poorly differentiated cells occasionally lose the ability to produce calcitonin.¹

MTC cells do not effectively concentrate radioactive iodine and typically do not respond to cytotoxic chemotherapy. For metastatic MTC, the overall survival rate is only 25% at 5 years.⁴ Novel approaches currently under investigation include targeted agents such as motesanib, sorafenib, sunitinib, and vandetanib, which inhibit the Ret and vascular endothelial growth factor (VEGF) receptor (VEGFR) tyrosine kinases.⁵⁻¹² Sorafenib is a multikinase inhibitor with potent activity against Raf, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor, and Ret kinases.¹³⁻¹⁵ Sorafenib is currently approved by the US Food and Drug Administration

for renal cell and hepatocellular carcinomas. Clinical activity has also been reported in patients with metastatic, radioiodine nonresponsive, differentiated thyroid carcinomas.^{7,15,16} In addition, sorafenib inhibited the growth of TT cells (C634R *RET* mutation–positive MTC cell line) in vitro and in vivo and inhibited wild-type and mutant Ret (634, 804, and 918 mutants) kinase activity.¹⁵ Because of the critical role of constitutive Ret signaling in MTC and the antitumor activity of sorafenib against MTC cells shown in preclinical models, we conducted this phase II clinical trial to investigate the activity of sorafenib in patients with advanced MTC.

PATIENTS AND METHODS

Patients

Patients with histologically confirmed metastatic or locally advanced MTC were enrolled onto either arm A (hereditary MTC based on germline *RET*-positive genotype) or arm B (sporadic MTC). Measurable disease; age ≥ 18 years; Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate bone marrow, hepatic, and renal function were required. Patients were not excluded based on the number and type of prior therapies received, with the exception of prior targeted therapy with sorafenib, vandetanib, or motesanib. Patients on therapeutic-dose anticoagulation were also excluded. The study was approved by the institutional review boards at both The Ohio State University (OSU) and Washington University.

Study Design

Sorafenib was administered at the dose of 400 mg orally twice daily on a continuous basis. Blood pressure was monitored and recorded by the patient at least weekly until stable or at least for the first 4 weeks. Physical examination, CBC count, and serum chemistries were performed at baseline and every 4 weeks for the first 24 weeks and then every 8 weeks. At each visit, patients were assessed for adverse events (AEs), concomitant medications, and compliance using patient diaries and pill count. AEs were graded using the Common Terminology Criteria for Adverse Events version 3.0.¹⁷ Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed within 4 weeks before treatment and repeated every 8 weeks thereafter. Triple-phase CT or MRI scans were required for evaluation of liver metastasis. Objective response was assessed using Response Evaluation Criteria for Solid Tumors (RECIST) version 1.0.¹⁸

In the event of any grade 3 or 4 drug-related nonhematologic AEs, recurrent grade 2 drug-related nonhematologic AEs, or grade ≥ 2 hand-foot-skin reactions (HFSRs), therapy was held until the AEs had resolved to grade ≤ 1 . On resolution of the AEs to grade ≤ 1 , sorafenib was resumed at a reduced daily dose of 400 or 600 mg, with the provision to re-escalate to the full dose as tolerated per investigator's discretion. Sorafenib was continued until progressive disease (PD) with no clinical benefit, discontinuation of sorafenib for any reason for ≥ 21 days, or patient withdrawal. Patients with evidence of clinical benefit (defined as symptomatic or tumor marker improvement, decreased tumor burden compared with baseline, or limited progression in nontarget lesion treated with radiation or surgery) despite PD per RECIST were allowed to continue sorafenib.

Correlative Studies

Serum calcitonin and CEA levels were obtained at baseline, every 8 weeks during treatment, and within 2 to 4 weeks after completion of treatment. Functional imaging with dynamic contrast-enhanced (DCE) MRI and combined [¹⁸F]fluorodeoxyglucose positron emission tomography (PET)/CT was performed at the discretion of the treating physician. The use of DCE-MRI and PET/CT was exploratory to evaluate tumor perfusion as a surrogate of the antiangiogenic activity of sorafenib and to evaluate standard uptake values (SUVs) as a tool to assess response, respectively. PET/CT imaging was performed 75 $\pm$ 10 minutes after [¹⁸F]fluorodeoxyglucose injection on a Siemens Biograph-16 combined PET/CT scanner (Siemens, Munich, Germany). All SUVs were normalized to body weight, and response to therapy was determined by the change in SUV for scans acquired before and during therapy.

In all patients, *RET* genotyping from peripheral blood was performed as a part of the standard of care evaluation. In patients with sporadic MTC, *RET* genotyping was also performed on DNA isolated from tumor tissue obtained from either previous surgery or biopsy (Appendix, online only). Paired tumor fine-needle aspiration biopsy samples (before treatment and at 8 weeks after treatment if patients had disease that could be biopsied and were willing to undergo biopsies for research purposes) were obtained to evaluate the degree of Ret-Ras-MAPK signaling inhibition by sorafenib (Appendix).

Statistical Analysis

The primary end point was to assess the objective response rate using RECIST. The Simon minimax two-stage design¹⁹ was used to evaluate a null hypothesis that the true objective response rate (ORR) was $\leq 10\%$ and an alternative hypothesis that the ORR was $\geq 30\%$, with a type I error (α) of 0.10 and type II error (β) of 0.10. The target accrual was 16 patients to each arm in the first stage, with an additional nine patients to be enrolled in the second stage if ≥ 2 responses were observed. The secondary end points were to assess the toxicity of sorafenib and to correlate tumor response with serum tumor marker changes, functional imaging, and the presence and type of *RET* mutations. Actuarial survival curves were estimated using the Kaplan-Meier method, and 95% CIs for the medians were provided for progression-free survival (PFS) and overall survival.

RESULTS

Patients

Between November 2006 and January 2008, 16 patients were enrolled onto arm B from OSU (Fig 1, Table 1). Five patients were enrolled onto arm A from OSU and Washington University. Arm A was terminated on September 10, 2009, because of poor accrual for this rare cancer and availability of several competing trials in the United States. We report the data on all patients collected through April 15, 2009.

Treatment Administration

At the time of data analysis, seven patients remained on study, whereas 14 patients came off therapy for the following reasons: arm B, six patients with PD, one clinical progression, and three AEs including one grade 5 event; and arm A, one AE, one patient withdrawal, one discontinuation of sorafenib for more than 21 days, and one loss of insurance coverage. Progression was noted in various metastatic sites

Fig 1. CONSORT diagram. MTC, medullary thyroid carcinoma; MEN-2A, multiple endocrine neoplasia type 2A; MEN-2B, multiple endocrine neoplasia type 2B; FMTC, familial medullary thyroid carcinoma; PO, oral; BID, twice a day.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Arm B: Sporadic MTC (n = 16)		Arm A: Hereditary MTC (n = 5)	
	No. of Patients	%	No. of Patients	
Age, years				
Median	60		49	
Range	39-72		21-70	
Sex				
Male	11	69	5	
Female	5	31	0	
Race				
White	13	81	5	
Nonwhite	3	19	0	
Prior therapy				
Surgery	15	94	5	
Chemotherapy	3	19	0	
Radiation therapy	8	50	5	
Site of metastasis				
Lymph node	16	100	3	
Liver	9	56	4	
Bone	11	69	2	
Lung	6	38	1	
Baseline calcitonin level, pg/mL				
Median	8,379		8,056	
Range	123-33,900		42-50,400	
Baseline RECIST measurement, cm				
Median	12		8.9	
Range	3.5-42.3		7-18.7	
Disease status at study entry*				
Stable disease $\geq$ 12 months	4	25	3	
Progressive disease < 12 months	10	62	0	
New diagnosis	2	13	2	

Abbreviations: MTC, medullary thyroid carcinoma; RECIST, Response Evaluation Criteria for Solid Tumors.

*Disease status at study entry was evaluated retrospectively and determined by RECIST, except for three patients in arm B (two with progressive disease and one with stable disease), whose disease status was determined by increasing calcitonin levels.

including lymph nodes, bone, and liver, with no specific site of metastasis accounting for PD. The median duration of sorafenib therapy was 15 months (range, 1 to 28.2 months). Sorafenib was administered at 600 mg/d during 55% (150 of 274 months of therapy in 21 patients) of the time on this trial. Sixteen patients (76%) required a dose reduction as a result AEs (HFSR, $n = 5$; diarrhea, $n = 3$; HFSR and hypertension, $n = 2$; HFSR and diarrhea, $n = 1$; hypertension, $n = 2$; other, $n = 3$), typically within the first 2 months of therapy. Both patients with partial response (PR) required dose reduction to 600 mg/d during first 2 months and thereafter were maintained at this dose. Although most patients were maintained at their reduced doses, six patients were re-escalated and maintained at a higher dose (two patients from 600 to 800 mg/d and four patients from 400 to 600 mg/d).

Objective Response

Among 15 evaluable arm B patients, all patients experienced some measurable degree of tumor shrinkage. In arm B, one patient achieved PR (PR duration of 20.7 months at data cutoff point), 14

patients had stable disease (SD; including eight patients with durable SD $\geq$ 15 months), and one patient who was nonevaluable for RECIST response had clinical PD (Fig 2). In a post hoc analysis of 10 arm B patients with PD within 12 months before study, one patient had PR of 21+ months, four patients had SD $\geq$ 15 months, four patients had SD $\leq$ 6 months, and one patient had clinical PD. For arm B, the median PFS time was 17.9 months, and the median overall survival time was not reached at the time of data analysis. As a result of

Fig 2. (A) Waterfall plot of Response Evaluation Criteria in Solid Tumors (RECIST) responses for arm B patients (maximum percentage of tumor reduction for target lesions by RECIST). Each bar represents an individual patient evaluable for RECIST response on arm B ($n = 15$). (*) Patients with *RET* M918T mutation. SD, stable disease; PR, partial response. (B) Progression-free survival for arm B patients. The median progression-free survival time is 17.9 months (95% CI, 8.0 months to not available). (C) Overall survival for arm B patients. The median overall survival was not estimable at the data analysis cutoff point.

Table 2. Tumor Response According to RECIST

Response	Arm B: Sporadic MTC (n = 16)		Arm A: Hereditary MTC (n = 5)*
	No. of Patients	%	No. of Patients
Evaluable patients	15	94	5
Nonevaluable patients	1†	6	0
PR	1	6	1
95% CI, %	0.2 to 30		NR
Time to PR, months	2		10
Duration of PR, months	20.7		8.9
SD	14	88	4
95% CI, %	61.7 to 99.5		NR
Maximum percentage of tumor reduction for target lesions	15	94	5
≥ 30% decrease	1		1
> 20%-29% decrease	2		1
> 10%-20% decrease	7		2
0%-10% decrease	5		1
Durable SD for ≥ 15 months	8	50	1
95% CI, %	24.7 to 75.4		NR
Durable SD for 6-12 months	1	6	1
Kaplan-Meier estimate of median progression-free survival, months	17.9		NR
95% CI	8 to NR		
Kaplan-Meier estimate of median overall survival	NR		NR

Abbreviations: RECIST, Response Evaluation Criteria for Solid Tumors; MTC, medullary thyroid carcinoma; PR, partial response; NR, not reportable; SD, stable disease.

*Because of small sample size and premature termination of accrual to arm A, results are only preliminary and not presented in percentages.

†One patient was taken off study at 6 weeks for clinical progression and did not have follow-up scans for RECIST evaluation.

premature termination of accrual to arm A, results reported (Tables 2 and 3) in five arm A patients are only preliminary.

AEs

As shown in Table 4, the most common grade 1 to 2 AEs included diarrhea, oral cavity pain, HFSR, alopecia, hypertension, non-HFSR rash, muscle pain or cramping, and cytopenias. Of 15 patients with grade 1 to 2 diarrhea, 11 had new onset of diarrhea, two had worsening of baseline diarrhea, and two had no change in the baseline diarrhea. Grade 3 AEs occurred in eight patients and included hypertension, HFSR, diarrhea, joint pain, infections, thrombocytopenia, and hyponatremia. Of the two patients with grade 3 diarrhea, one had worsening of baseline grade 1 diarrhea, whereas the other patient developed new-onset diarrhea. Grade 4 AEs included pulmonary embolus and hypokalemia. There was one grade 5 event of death in a patient in arm B with an adrenocorticotrophic hormone–producing metastatic MTC who had a sepsis-like clinical picture including renal failure, hyperkalemia, and disseminated intravascular coagulation. On autopsy, no obvious bowel perforation was found, although there was a segment of hemorrhagic and necrotic small bowel and widespread *Clostridium* infection detected.

Tumor Marker Response

Twenty patients had calcitonin and CEA tumor marker measurements at both baseline and at least one other time point 8 weeks after

study initiation. As shown in Table 3 and Figure 3, 17 patients had a decrease in either the calcitonin or CEA level, and 11 patients had a decrease in both tumor markers. The majority of patients (75%) showed the largest decrease in calcitonin levels after the first 2 months of therapy. However, neither the timing nor the degree of tumor marker response significantly correlated with the degree or duration of RECIST response.

Tumor RET Genotype

RET mutational analysis of all patients is reported in Table 3. Germline RET mutations were confirmed in all five of the patients with hereditary MTC before study entry. Of the 16 patients with sporadic MTC, 12 had tumor DNA samples of sufficient quantity for RET genotype testing. Ten of 12 patients tested were positive for a RET mutation (nine with M918T and one with C634R). All patients with the RET M918T mutation had had PD within 12 months of study entry or were newly diagnosed just before study entry. Of the two patients with PR, one had hereditary MTC with the RET C634R mutation, and the other had sporadic MTC with the RET M918T mutation. Of the two patients who were negative for the RET M918T and C634R mutations, one had durable SD of 15 months, and the other had clinical progression.

Pharmacodynamic Studies

Paired tumor biopsy samples were obtained from neck lymph nodes under ultrasound guidance from five arm B patients to analyze changes in VEGF expression and in phosphorylation of Ret, VEGFR, Erk, and Akt. However, because of low tumor cellularity in the samples obtained, such evaluation was not possible.

PET/CT Imaging Response

Maximum SUV (SUV_{max}) data were calculated for 70 target lesions from nine patients on this study. At baseline, the median number of index lesions per patient identified was eight lesions (range, three to 17 lesions), and the median SUV_{max} was 3.73 (range, 2.84 to 4.63). At the 8-week follow-up, the median SUV_{max} was 2.94 (range, 2.24 to 3.88). The correlation between changes in SUV_{max} and objective tumor response was not statistically significant.

Tumor Perfusion Response

DCE-MRI scans were available and evaluable in 10 patients. Within the first 24 weeks of therapy, the median decrease in exchange rate (K_{ep}) in index lesions in nine patients was 79% (range, 25% to 96%) compared with baseline. There was no decrease in K_{ep} in one patient. The median decrease in amplitude (Amp) in index lesions in six patients was 31% (range, 10% to 51%), whereas there was no decrease in Amp for four patients. Nine patients had SD, and one patient had PR. In the patient with PR, the decrease in Amp was 51%, and the decrease in K_{ep} was 64%. For all patients evaluated, there was no correlation between the magnitude of decrease for both K_{ep} and Amp and objective tumor response.

DISCUSSION

In addition to having inhibitory activity against the Raf, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor B, FLT-3, and c-kit kinases, sorafenib also inhibits the Ret kinase, making it a rational

Table 3. RECIST Response and Correlative Studies

Patient No.	Disease Status at Study Entry*	RET Mutational Status	Best RECIST Response	Duration of RECIST Response (months)	Best RECIST Change From Baseline (%)†	Best Calcitonin Response (%)	Best CEA Response (%)
Arm B (sporadic MTC)							
006	PD	M918T	SD	1.9	−9	39	111
007	PD	M918T	SD	15.8	−17	4	28
008	SD	Not tested	SD	5.2	−5.7	30	17
009	PD	M918T	SD	1.9	−8	−54	15
010	PD	M918T	SD	28.2	−9.3	−46	−40
011	SD	Not tested	SD	21.8	−23.8	−45	0
012	SD	Not tested	SD	24.9	−11.5	−30	−27
013	New diagnosis	M918T	SD	23.5	−27	−43	−46
014	PD‡	Negative	NA (clinical PD)	NA	NA§	NA	NA
015	PD‡	M918T	PR	20.7	−77	−89	−45
016	New diagnosis	M918T	SD	3.9	−19	30	−48
017	PD	Not tested	SD	1.9	−11	−20	26
018	PD	Negative	SD	15.3	−19	−70	−43
019	SD‡	C634R	SD	17.2	−7.7	−70	−16
020	PD	M918T	SD	15.5	−11.5	−88	−71
021	PD	M918T	SD	6.1	−15.5	−71	13
Arm A (hereditary MTC)							
001	SD	C634Y	SD	6	−4.5	−72	100
002	SD	C634R	PR	8.9	−36	−74	−10
003	SD	M918T	SD	15	−13	−49	−40
004	New diagnosis	C634F	SD	5.9	−19	−48	−46
005	New diagnosis	C618R	SD	3.5	−21	−82	−30

Abbreviations: RECIST, Response Evaluation Criteria for Solid Tumors; CEA, carcinoembryonic antigen; MTC, medullary thyroid carcinoma; PD, progressive disease; SD, stable disease; NA, not assessable; PR, partial response.

*Disease status within 12 months before study entry. Data were collected retrospectively.

†Best percent change from baseline of the sum of the longest diameter of index lesions.

‡Disease status at study entry for these three patients was determined by calcitonin levels. For all other patients, disease status was determined by RECIST.

§NA because patient was taken off study at 6 weeks for clinical progression and did not have follow-up scans for RECIST evaluation.

therapy for *RET*-activated thyroid cancers such as MTC. In this study, we predetermined that sorafenib would be worthy of further study if the true response probability or target response rate was $\geq 30\%$. Accrual to the hereditary MTC arm was prematurely terminated, and conclusions about efficacy of sorafenib in patients with hereditary MTC cannot be drawn. In the sporadic MTC arm, the target of two objective responses out of 16 patients treated in the first stage was not reached. Although only one PR was observed in patients with sporadic MTC, 50% of patients demonstrated SD ≥ 15 months, with tumor shrinkage ranging from 8% to 27%. Furthermore, of the 10 patients with PD in the 12 months before study entry per a post hoc analysis, one patient had PR of 21+ months, and four patients had SD ≥ 15 months. Although this suggestion of prolonged SD is encouraging, it is based on post hoc analysis of a small subset of patients in this trial.

Our findings of a low PR rate but high rate of SD were also observed in the recent phase II studies of motesanib, a VEGFR inhibitor, in patients with sporadic MTC and vandetanib, an inhibitor of Ret, epidermal growth factor receptor, and VEGFR, in patients with hereditary MTC.^{21,22} Limitations of RECIST for assessing response to small-molecule kinase inhibitors are well recognized, and PR may not be the most accurate way to assess response to such therapies.²²⁻²⁴ Selection of the proper primary end point in studies evaluating efficacy of tyrosine kinase inhibitors remains challenging, especially in patients with MTC, where the natural history of disease is heterogeneous and historical controls for median PFS are not well defined. Attempts have been made to identify high-risk patients with sporadic MTC. For

example, MTCs with the *RET* 918 mutation are generally associated with an aggressive clinical course.²⁵ Although patients in our sporadic MTC arm were not preselected for the *RET* 918 mutation, tumors from nine of 12 patients tested were positive for this particular mutation, indicating that the patients in this study had more aggressive tumors compared with what is generally expected for sporadic MTC. This tendency toward tumors with an aggressive course is reflected in our study population in that all of the patients with sporadic MTC with the *RET* 918 mutation had had PD within 12 months of study entry or were newly diagnosed with advanced disease at study entry. Our patients also had high tumor burden in visceral metastasis (Table 1), and 69% of patients had had prior radiation or chemotherapy, suggesting clinically aggressive tumor behavior.

A decrease of either calcitonin or CEA, or both, was observed in the majority of patients on this study. However, neither baseline tumor marker level nor the degree of tumor marker response significantly correlated with the degree or duration of RECIST response. Whether calcitonin decreases are related to transcription inhibition of calcitonin or tumor shrinkage remains unclear. The Ret kinase inhibitor NVP-AST487 was shown to inhibit calcitonin gene expression and transcription in TT cell xenografts, leading to lowered plasma calcitonin levels shortly after treatment.²⁶

Sorafenib was reasonably well tolerated in this study. Fourteen patients were treated with sorafenib for ≥ 6 months, with a median duration of treatment of 15 months. In general, the AEs observed were

Table 4. Treatment-Related Adverse Events Possibly, Probably, or Definitely Attributed to Sorafenib

Adverse Event	Grade 1 or 2		Grade $\geq$ 3	
	No. of Patients	%	No. of Patients	%
Constitutional				
Weight loss	10	48	0	0
Anorexia	8	38	0	0
Fatigue	7	33	0	0
Taste changes	4	19	0	0
Chills	1	5	0	0
GI				
Diarrhea	15	71	2	10
Oral cavity pain	13	62	0	0
Mucositis	10	48	0	0
Flatulence	8	38	0	0
Abdominal pain or cramping	6	29	0	0
Abdominal bloating	4	19	0	0
Nausea	3	14	0	0
Heartburn	2	10	0	0
Dermatologic				
HFSR	16	76	3	14
Alopecia	16	76	0	0
Rash (non-HFSR)	14	67	0	0
Nail changes	10	48	0	0
Dry skin/scalp	10	48	0	0
Skin lesions/sores (non-HFSR)	8	38	0	0
Scalp pruritus	7	33	0	0
Photosensitivity	3	14	0	0
Ruddy complexion	1	5	0	0
Vascular				
Hypertension	9	43	2	10
Flushing	9	43	0	0
Epistaxis	3	14	0	0
Pulmonary embolism	0	0	1	5
Hemoptysis	1	5	0	0
Puffy face	1	5	0	0
Breast swelling	1	5	0	0
Musculoskeletal				
Muscle pain or cramping	11	52	0	0
Joint pain	8	38	1	5
Scalp pain	7	33	0	0
Stiff neck	1	5	0	0
Neurologic				
Dizziness	3	14	0	0
Memory loss	1	5	0	0
Headache	1	5	0	0
Sensory neuropathy	1	5	0	0
Visual floaters	1	5	0	0
Ataxia/unsteadiness	1	5	0	0
Arm weakness	1	5	0	0
Auditory hallucinations	1	5	0	0
Infection	4	19	2	10
Hoarseness	3	14	0	0
Tachycardia	1	5	0	0
Hematologic				
Leukopenia	11	52	0	0
Neutropenia	7	33	0	0
Lymphopenia	3	14	0	0
Thrombocytopenia	10	48	1	5
Anemia	8	38	0	0

(continued in next column)

Table 4. Treatment-Related Adverse Events Possibly, Probably, or Definitely Attributed to Sorafenib (continued)

Adverse Event	Grade 1 or 2		Grade $\geq$ 3	
	No. of Patients	%	No. of Patients	%
Liver function elevation				
LDH	13	62	0	0
AST	9	43	0	0
ALT	8	38	0	0
Bilirubin	4	19	0	0
Alkaline phosphatase	3	14	0	0
Serum chemistry				
Hypophosphatemia	12	57	0	0
Hypocalcemia	12	57	0	0
Hyponatremia	11	52	1	5
Hyperglycemia	4	19	0	0
Increased creatinine	1	5	0	0
Hypernatremia	1	5	0	0

NOTE. See Results for grade 4 and 5 adverse events.

Abbreviations: HFSR, hand-foot-skin reaction; LDH, lactate dehydrogenase.

mostly low grade and were similar to toxicities previously reported.^{7,16,24} Rare serious toxicities of sorafenib, including bowel perforation, have been described; one death occurred in our study that was possibly related to such an AE. These rare but fatal AEs must be taken

Fig 3. Comparison of the best Response Evaluation Criteria in Solid Tumors (RECIST) and serum (A) calcitonin and (B) carcinoembryonic antigen (CEA) changes from baseline for arm B patients. RECIST response refers to the change from baseline in the sum of the diameter of all indexed lesions.

into account for assessing risk versus benefit when offering sorafenib to patients with metastatic MTC. Most of the observed AEs were managed effectively with dose reduction and symptomatic therapy.

In our previous study of sorafenib in differentiated thyroid cancers, four of 10 paired biopsy samples demonstrated a decrease of immunoactive pVEGFR, pERK, and VEGF, whereas two other samples showed decreased pAkt immunoactivity. All of the patients who demonstrated high basal levels of pERK and pVEGFR had significant inhibition with therapy.¹⁶ However, in the present study, we were unable to evaluate paired tumor biopsy samples for such pharmacodynamic studies. Although we do not know the true targets of sorafenib or the degree of contribution from Ret inhibition, VEGFR inhibition seems to play an important role. VEGFR is a common target among kinase inhibitors such as motesanib, sorafenib, vandetanib, and XL-184 that have shown antitumor activity in patients with MTC.^{6-9,12,16,20,21,27-29} Although the hypervascular nature of MTC is well known, studies evaluating a role of VEGF expression in MTC involve small sample sizes and reveal variable results.^{6,29-31}

In summary, sorafenib is a reasonably well-tolerated oral therapy that offers clinical benefit and may be an option for patients with sporadic metastatic MTC who are not able to participate in clinical trials. Early recognition and prompt management of the expected AEs of sorafenib will allow more patients to continue on therapy as long as they are achieving clinical benefit. Future studies should evaluate the predictors of response to sorafenib and combination therapies to enhance the degree and duration of response.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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