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ORIGINAL REPORT

Phase II Trial of Sorafenib in Patients With Metastatic Breast Cancer Previously Exposed to Anthracyclines or Taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336

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ABSTRACT

Purpose
We conducted a cooperative group phase II study to assess antitumor activity and toxicity of sorafenib in patients with metastatic breast cancer (MBC) who had received prior treatment for their disease.

Patient and Methods
Patients were eligible if they had measurable disease and had previously received an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting. The primary end point of the study was tumor response per Response Evaluation Criteria in Solid Tumors (RECIST). The study was designed in two stages. Sorafenib was administered as 400 mg twice daily on days 1 through 28 of each 4-week cycle.

Results
Twenty-three patients were enrolled with a median age of 54 years (range, 37 to 70 years). Twenty-two (96%) had prior anthracycline treatment and 16 (70%) had prior taxane treatment. Patients received sorafenib for a median of two cycles (range, one to 15 cycles) with a median follow-up of 2.4 years (range, 2.2 to 2.6 years). There were no grade 4 toxicities and few grade 3 toxicities. Among the 20 patients eligible for efficacy analysis, no patients experienced a partial response or complete response per RECIST criteria. Thus, the trial stopped at the end of the first stage per study design. Two patients (10%; 90% CI, 1.8% to 28.3%) achieved stable disease lasting longer than 6 months.

Conclusion
Sorafenib as a single agent, although well tolerated, did not exhibit activity when measured by tumor shrinkage in patients with MBC who had received prior treatment. Further research should focus on combinations with standard therapy and end points more sensitive to effects of targeted agents, such as disease stabilization.

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INTRODUCTION

Breast carcinoma is the most common malignancy of women around the world.[1a] Unfortunately, despite advances in adjuvant treatment for early-stage breast cancer, many women develop tumor relapse. First-line treatments for metastatic disease with single-agent hormonal or chemotherapy regimens produce response rates between 20% and 40%.[1,2] The median time to progression (TTP) for those women who respond is 3 to 8 months. In the second-line setting, response rates are only 10% to 20%. The development and testing of novel agents targeting pathways thought to be involved in the pathogenesis of metastatic breast cancer (MBC) are therefore warranted.

The Ras/raf/mitogen-activated protein kinase signaling pathway and the phosphoinositide-3 kinase/mammalian target of rapamycin pathway influence transcription and cell-cycle transition in human breast cancer cells. These signaling pathways are important mediators of responses to growth signals and angiogenic factors and are often aberrantly activated in breast cancer cells. Therefore, inhibition of these pathways may be of clinical benefit.[3] Sorafenib (BAY 43-9006) is an oral drug capable of inhibiting several receptor tyrosine kinases that are involved in tumor progression and

angiogenesis including the vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptors α and β, RET, Flt3, and c-KIT.[4,5] Sorafenib is approved for the treatment of metastatic renal cell carcinoma (RCC) and advanced hepatocellular carcinoma (HCC).

Sorafenib has been evaluated in more than 10,000 patients in a variety of clinical trials including several large phase III studies in renal cell carcinoma[6] and hepatocellular carcinoma as a single agent,[7] and in phase II and phase III single agent or combination trials with chemotherapy in non–small-cell lung cancer, metastatic melanoma, sarcoma, thyroid cancer, head and neck cancer, and other tumor types.[8-12] We present here the results of a cooperative group phase II trial of sorafenib as a single agent in patients with previously treated MBC conducted by the North Central Cancer Treatment Group (NCCTG).

PATIENTS AND METHODS

Patient Selection

Eligibility requirements included men or women with histologic or cytologic confirmation of breast cancer with clinical evidence of metastatic disease if they met the following criteria: candidacy for first- or second-line chemotherapy for metastatic disease; previous treatment with an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting; and measurable disease defined as at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST). Unlimited prior hormonal therapy was allowed in the neoadjuvant, adjuvant, or metastatic setting; human epidermal growth factor receptor 2 (HER-2)-positive or -negative disease was allowed, but patients with HER-2–positive disease must have had prior treatment containing trastuzumab as per standard of care unless the treating physician felt that trastuzumab was not indicated.

Patients were also required to be at least 18 years old; have a life expectancy of at least 3 months; and have an Eastern Cooperative Oncology Group performance score of 0 or 1. Eligibility required adequate hematologic function (WBC $\geq$ 3,000/mm^3; neutrophil count $\geq$ 1,500/mm^3; platelets $\geq$ 100,000 mm^3; hemoglobin $\geq$ 8.5 g/dL); hepatocellular function (total bilirubin $\leq$ 1.5$\times$ the upper limit of normal [ULN]; alkaline phosphatase $\leq$ 3$\times$ ULN; AST $\leq$ 3$\times$ ULN); and renal function (creatinine $\leq$ 1.5$\times$ ULN). Additionally study entry criteria called for calcium, prothrombin, international normalized ratio of prothrombin time, and partial thromboplastin time all to be at or below ULN.

The study was approved by local institutional review boards, and written informed consents were obtained from all patients before they were randomly assigned.

Drug Administration

A starting dose of 400 mg of sorafenib was administered orally two times daily on days 1 through 28 of each 4-week cycle (sorafenib was supplied to the NCCTG by the National Cancer Institute [NCI]; sorafenib was provided to the NCI by Bayer Corporation [Pittsburgh, PA]/Onyx Pharmaceuticals Inc [Emeryville, CA] under a Clinical Trials Agreement between Bayer/Onyx and the Division of Cancer Treatment and Diagnosis, NCI). A level-1 dose reduction was 400 mg once daily. Dose modifications were based on interval adverse events (grade 4 neutropenia and/or thrombocytopenia, persistent symptomatic grade 2 or any grade 3 arterial hypertension, grade 2 to 3 hand and foot syndrome, and any other grade 3-4 nonhematologic adverse event felt to be related to study drug). Treatment continued until disease progression or excessive toxicity.

Response Assessment and Criteria

Patient evaluations included complete patient histories, physical examinations, measurement of the indicator lesion(s) per RECIST (by conventional computed tomography [CT] or magnetic resonance imaging scans if index lesion[s] $\geq$ 2.0 cm or by spiral CT scan if $\geq$ 1.0 cm), weight, performance score, hematologic and chemistry groups, and research blood samples were performed before random assignment and subsequent treatment cycles. A chest x-ray or CT, serum or urine pregnancy test, and research tissue sample (primary tumor specimen for evaluation of phosphorylated ERK1/2 by immunohistochemistry), were required before random assignment. Blood pressure was taken weekly during the first 4-week cycle of treatment and before each subsequent cycle of treatment. Hematologic and chemistry groups were also required 7 to 10 days after day 1 of cycle 1 and at termination of treatment. A research blood sample was also required at termination of treatment (for evaluation of circulating tumor cells by immunohistochemistry for phosphorylated ERK1/2, phosphorylated AKT, and cleaved caspase 3). The data from these correlative studies are being compiled in a larger study and will be reported separately.

End Point and Statistical Analysis

The primary end point of the study was tumor response as assessed by RECIST. The secondary end point was to examine the distributions of disease progression and survival times. A two-stage design was performed with a possible total of 40 patients: If more than one confirmed response (complete response [CR] or partial response [PR]) was seen in the first 20 eligible patients (stage 1), another 20 patients would be enrolled (stage 2). This design was chosen such that at a .10 significance level, there would be a 91% chance of detecting a tumor response rate of at least 20% and a response rate of 5% or less would lead to the conclusion that the regimen lacks antitumor activity in this patient population. A treatment success was defined as either a CR or PR observed on two consecutive evaluations at least 4 weeks apart. The true response rate was estimated by the proportion of eligible patients who achieved a confirmed CR or PR by RECIST. Ninety percent CIs for the true response rates were calculated according to the Duffy-Santer approach.[13] Survival time was defined to be the time from registration to the date of death resulting from any cause. Time to disease progression was defined to be the time from registration to the date of disease progression. Patients who died without disease progression were considered to have had tumor progression at the time of death. The distribution of time to progression and survival time was estimated using the Kaplan-Meier method.[14]

The study was temporarily closed to accrual after 20 eligible patients were enrolled and an analysis was conducted 6 months after the last eligible patient was enrolled to ascertain whether there was sufficient activity to open enrollment to the second stage of the trial.

RESULTS

Patient Characteristics

Twenty-three patients were enrolled between November 2004 and June 2005. Three (13%) of the 23 patients were declared ineligible because they had more than one prior chemotherapy regimen for metastatic disease. All 23 patients were included in all analyses except efficacy analysis as stated per study design. The patient characteristics of the 23 patients are presented in Table 1. Twenty-two (96%) of the all-female cohort were postmenopausal, and 15 (65%) had visceral metastasis. Twenty-two (96%) patients had received prior anthracycline treatment: three (13%) in the neoadjuvant setting, 18 (78%) in the adjuvant setting, and one (4%) in the metastatic setting. Sixteen patients (70%) had received prior taxane treatment: three (13%) in the neoadjuvant setting, seven (30%) in the adjuvant setting, five (22%) in the metastatic setting, and one (4%) in both the adjuvant and metastatic settings. Nine patients (39%) had received prior hormonal therapy and 10 (44%) had received prior chemotherapy for metastatic disease. Fourteen patients (61%) had a relapse-free interval of 12 months or more before enrollment and three patients (13%) were HER-2 positive.

Table 1. Patient Characteristics at Entry (N = 23)

Characteristic	No.	%
Age, years		
Median	54	
Range	37-70	
Performance status		
0	18	78
1	5	22
Race		
African American	1	4
White	22	96
Prior chemotherapy for MBC		
Yes	10	43
No	13	57
Prior anthracycline		
Neoadjuvant	3	13
Adjuvant	18	78
Metastatic	1	4
None	1	4
Menopausal status		
Premenopausal	1	4
Postmenopausal	22	96
HER-2 status at diagnosis		
FISH amplified	0	0
FISH not amplified	4	17
IHC strongly positive	3	13
Moderately positive	0	0
Weakly positive	3	13
Negative	11	48
Not done	2	9
Length of relapse-free interval, months		
< 3	4	17
3-6	4	17
6-12	1	4
> 12	14	61
Prior hormonal treatment		
Yes	9	39
No	14	61
Prior taxane		
Neoadjuvant	3	13
Adjuvant	7	30
Metastatic	5	22
Adjuvant and metastatic	1	4
None	7	30
Dominant disease		
Soft tissue	7	30
Visceral	15	65
Bone	1	4
Estrogen status		
Negative	12	52
Positive	10	44
Unknown	1	4
Progesterone status		
Negative	13	57
Positive	9	39
Unknown	1	4

Abbreviations: IHC, immunohistochemistry; FISH, fluorescent in situ hybridization; HER-2, human epidermal growth factor 2; MBC, metastatic breast cancer.

Safety

Eighty-eight cycles of treatment were administered throughout the study with a median of two cycles (range, one to 15 cycle). The median sorafenib dose-intensity administered was 371 mg twice daily (93% of full dose) during cycle 1 and 357 mg twice daily (89% of full dose) during cycle 2. Seventy percent of the patients on treatment during cycle 1 received 80% or more of the full dose (intended dose). The most common reason for a dose reduction was dermatitis/skin rash (three patients) and hand/foot skin reaction (two patients). Other reasons for dose reductions included hypertension (one patient), cramping in hands and feet (one patient), and patient decision (one patient). All patients have discontinued treatment at this time. The reasons for discontinuing treatment included disease progression (n = 18, 90%), adverse events (n = 1, 5%; grade 2 skin rash), and patient refusal (n = 1, 5%).

Toxicity data were available for all 23 patients enrolled on study. Most toxicities were mild (grade 1 to 2) and manageable. Table 2 outlines all grade 1 to 2 toxicities with an incidence greater than 10%. The most common toxicity reported in the study was fatigue. There were no grade 4 toxicities and few grade 3 toxicities. The grade 3 toxicities included one incidence each of hand/foot skin reaction, acne, fatigue, neutropenia, cough, dyspnea, anorexia, wound infection, and partial thromboplastin time. There was one death that occurred within 30 days of last treatment, which was considered to be the result of disease progression.

Efficacy

Patients were followed until death or a median of 2.4 years (range, 2.2 to 2.6 years) among living patients. Among the 20 patients eligible for efficacy analysis, no patients experienced a partial response or complete response per RECIST. Thus, the trial stopped at the end of the first stage per study design. Two patients (10%; 90% CI, 1.8% to 28.3%) had stable disease lasting longer than 6 months. The 1-year overall survival rate was 70% (95% CI, 53% to 93%). The median progression-free survival (PFS) was 2.0 months (95% CI, 1.7 to 4.1

Table 2. Grade 1 and 2 Toxicities (hematologic and nonhematologic regardless of attribution) With Incidence > 10%

	Grade 1		Grade 2	
Toxicity	No.	%	No.	%
Fatigue	14	61	4	17
Acne NOS	8	35	4	17
Skin reaction, hand/foot	9	39	1	4
Alopecia	10	43	3	13
Anorexia	9	39	2	9
Diarrhea	9	39	2	9
Nausea	9	39	2	9
Hypertension	5	22	1	4
Dyspnea	3	13	3	13
Neurosensory	5	22	1	4
Pain, abdominal	5	22	0	0
Oral cavity MS CE	4	17	1	4
Leukopenia	1	4	3	13
Neutropenia	2	9	2	9
Weight loss	5	22	0	0
Dry skin	1	4	2	9
Constipation	2	9	1	4
Vomiting	3	13	0	0

Abbreviations: NOS, not otherwise specified; MS, mucositis/stomatitis; CE, clinical exam.

months). The PFS rates were 10% (95% CI, 3% to 37%) at 6 months, and 5% (95% CI, 1% to 34%) at 1 year.

DISCUSSION

Several strategies have been developed to target the Ras/raf/mitogen-activated protein kinase signaling pathway and the vascular endothelial growth factor pathway, potentially enabling the simultaneous blockade of tumor cell proliferation and angiogenesis as well as increasing tumor apoptosis. Sorafenib is a novel, oral multikinase inhibitor, capable of inhibiting both signaling pathways. In the current study, sorafenib was shown to be safe and well tolerated in patients with MBC who had received prior treatment. Most adverse events were grade 1 or 2; there were few grade 3 events and no grade 4 events. One patient discontinued therapy as a result of toxicity. Activity as assessed through measurable tumor response, however, was not observed.

Qualities of an ideal trial end point include that it is quantifiable, relevant, and sensitive to the effects of an intervention.[15-17] It is this last quality that, if not appropriately defined, may prematurely lead us to discontinue therapies that may be effective for our patients. Whether unidimensional tumor response is an appropriate measure of benefit for novel targeted agents such as sorafenib is of much debate. In two large randomized phase III trials in RCC and HCC, sorafenib was shown to significantly prolong PFS and/or overall survival, with negligible effects on tumor response. In the RCC trial, sorafenib doubled median PFS (hazard ratio [HR] = 0.44; 95% CI, 0.35 to 0.55; $P < .000001$) and increased overall survival [HR = 0.77; 95% CI, 0.63 to 0.95; $P = .02$) compared with placebo.[6] In the HCC trial, sorafenib significantly increased overall survival (HR = 0.69; 95% CI, 0.55 to 0.88; $P = .00058$) and time to progression (HR = 0.58; 95% CI, 0.44 to 0.74; $P = 000007$) compared with placebo.[7] Importantly, in both trials, the confirmed PR rate was 2%; there were no complete responses. These data suggest that the activity of sorafenib is mediated through disease stabilization processes rather than tumor shrinkage.

The activity of sorafenib in MBC, as assessed by disease stabilization, appears to be comparable with other single antiangiogenic agents. In another trial of sorafenib in 56 patients with heavily pretreated MBC (69% of patients had received more than three prior chemotherapy regimens for metastatic disease), 13% of patients had stable disease for 6 months or longer. There was one PR (2%).[18] In a phase I/II trial of bevacizumab in 75 patients with heavily pretreated MBC (40% of patients had received three or more prior chemotherapy regimens for metastatic disease), 16% of patients had stable disease or better at 5 months.[19] In a phase II trial of sunitinib in 64 patients with heavily pretreated MBC (52 patients had received prior adjuvant therapy and 61 had received chemotherapy in metastatic setting), 16% of patients had stable disease or better at 6 months.[20] Notwithstanding limitations of comparing separate trials, these trials suggest that as single antiangiogenic agents, they are only modestly effective in stabilizing disease in MBC.

The promise of antiangiogenic therapy in breast cancer is likely to be best realized in combination with standard background therapies. The trial of bevacizumab in combination with paclitaxel underscores this premise.[21] The safety profile of sorafenib makes it particularly suitable for combination therapy. In the current trial and in the previously mentioned trial by Bianchi et al,[18] there were few grade 3 adverse events (the most common were skin related). Importantly, there was only one case of grade 3 neutropenia in the current trial (4%) and no instances of grade 3 neutropenia in the other trial. The favorable safety profile, coupled with oral administration, may make future investigations of sorafenib in combination with other therapies, such as aromatase inhibitors, of particular scientific interest. Future trials of sorafenib in MBC that focus on combination therapy and measure PFS as a primary end point are warranted and are underway.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

Additional participating institutions include Meritcare Hospital CCOP, Fargo, ND (Preston D. Steen, MD); Geisinger Clinic & Medical Center CCOP, Danville, PA (Albert M. Bernath Jr, MD); Illinois Oncology Research Association CCOP, Peoria, IL (John W. Kugler, MD); Toledo Community Hospital Oncology Program CCOP, Toledo, OH (Paul L. Schaefer, MD); Michigan Cancer Research Consortium, Ann Arbor, MI (Philip J. Stella, MD); and Upstate Carolina CCOP, Spartanburg, SC (James D. Bearden III, MD).