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A Phase II Evaluation of Motesanib (AMG 706) in the Treatment of Persistent or Recurrent Ovarian, Fallopian Tube and Primary Peritoneal Carcinomas: A Gynecologic Oncology Group Study

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Abstract

Objectives—Vascular endothelial growth factors (VEGF) and their receptors have a critical role in stimulating the growth of ovarian cancer cells. Motesanib is a small molecule inhibitor of multiple receptor tyrosine kinases including VEGF receptors 1-3, as well as c-KIT and platelet-derived growth factor which are related to the VEGF family.

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CONFLICT OF INTEREST STATEMENT

The authors report that there are no conflicts of interest to declare.

Patients and Methods—Twenty-two eligible patients with recurrent ovarian, fallopian tube or primary peritoneal carcinoma were treated with an oral daily dose of 125 mg of motesanib. Peripheral blood was analyzed for circulating tumor cells (CTC) and circulating endothelial cells/ circulating endothelial progenitors (CEC/CEP), VEGF levels and cell-free circulating DNA (cfDNA).

Results—The study was abruptly halted after four patients developed posterior reversible encephalopathy syndrome. One patient had a partial response and seven patients had stable disease at the time they were removed from study treatment. Twelve of the 22 patients (50%) had indeterminate responses at trial closure. Early closure without clinical efficacy data precludes meaningful correlative studies.

Conclusions—The serious central nervous system toxicity observed in patients with recurrent ovarian cancer precluded full examination of this agent in this population. There were no clear cut explanations for the high incidence of this known class effect in the study population compared with patients with other cancers.

Keywords

ovarian; cancer; motesanib; antiangiogenesis; encephalopathy

INTRODUCTION

In 2010, approximately 22,000 women were diagnosed with epithelial ovarian carcinoma in the United States [1]. While most of these women initially achieved clinical complete responses, most relapse and ultimately die of their cancers [2]. Treatment of women with recurrent ovarian cancer remains a major challenge. Discovering new, effective therapeutic agents is essential for improving the outcome of these patients.

The pivotal role of vascular endothelial growth factor (VEGF) in ovarian cancer cell growth has been established [3]. Anti-VEGF therapy has been shown to have activity in patients with recurrent and primary disease [4-6]. Bevacizumab is a monoclonal antibody that binds to VEGF-A, prohibiting its binding to and subsequent activation of its receptor, VEGFR-2 [7]. There are multiple members of the VEGF receptor family such as VEGF receptors 1-3. Some small molecule multi-kinase inhibitors target all VEGF receptors. Examples include sorafenib and sunitinib, which have been approved for the treatment of renal cell carcinoma, hepatocellular carcinoma, and gastrointestinal stromal tumor (GIST).

Motesanib is an orally bioavailable inhibitor of numerous tyrosine kinases including VEGF receptors 1-3 but also c-KIT and platelet-derived growth factor receptor (PDGFR) which are related to the VEGF receptor family [7,8]. Motesanib inhibited human endothelial cell proliferation and the increase in vascular permeability induced by VEGF but not by fibroblast growth factor. Oral administration of motesanib markedly inhibited VEGF induced angiogenesis in the rat corneal model and induced regression of established A431 xenografts in mice. In two dose-finding trials, the maximum tolerated dose was determined to be 125 mg orally daily. Dose limiting toxicities (DLT) at 175 mg daily included encephalopathy, fatigue and hyperbilirubinemia (1 patient each). One other patient developed encephalopathy at 125 mg. Twenty percent of patients developed grade 3 hypertension that was successfully managed with antihypertensive agents [9]. The other trial did not escalate doses of motesanib beyond 125 mg orally daily based on the aforementioned trial. There were no DLTs. Although 60% of patients developed hypertension, only two of them experienced grade 3 motesanib related hypertension. The other patients were managed by administration of antihypertensive therapy without necessitating stopping study drug [10]. In a phase II trial involving 93 patients with

progressive locally advanced or metastatic radioiodine-resistant differentiated thyroid cancer, an overall response rate of 14% was observed with 67% of patients achieving stable disease (35% for at least 24 weeks)[11]. Median progression-free survival was 40 weeks. The most common toxicities included hypertension (25% grade3), diarrhea (13% grade 3) weight loss (5% grade 3) and fatigue (4% grade 3). Grade 4 events included cerebral hemorrhage, confusion, agitation, hypercalcemia, hyperuricemia, hypokalemia, and oliguria in one patient each. There were two treatment-related deaths due to pulmonary hemorrhage in patients with progressive disease. More recently, Benjamin and colleagues reported their experience with motesanib in 102 patients with gastrointestinal stromal tumors [12]. Similar to earlier trials, the most common treatment related grade 3 toxicities were hypertension (23%), fatigue (9%), and diarrhea (5%). There was one patient having hypertension and associated PRES. Several other investigators noted a high incidence of significant hypertension in patients being treated with motesanib [13-16].

Since chemotherapeutic agents have limited impact in patients with refractory ovarian cancer and given the recently demonstrated activity of antiangiogenic targeted therapy, it is reasonable to evaluate the utility of a multi-kinase inhibitor such as motesanib in this patient population.

PATIENTS AND METHODS

Patients and Treatment

Eligible patients had a histologically confirmed diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Patients were required to have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [17], a Gynecologic Oncology Group (GOG) performance status of 0-2, adequate bone marrow (absolute neutrophil count ≥ 1,500/μL, platelet count ≥ 100,000/μL), renal (serum creatinine ≤ 1.5 x the upper limit of normal), and hepatic function (total bilirubin ≤ 1.5 x the upper limit of normal, and transaminases and alkaline phosphatase ≤ 2.5 x the upper limit of normal). Patients were permitted to have received up to two prior cytotoxic regimens, but if patients had received only one, they were required to have a platinum-free interval of less than 12 months or have progressed during, or have persistent disease, after platinum-based therapy. Patients with prior radiation to more than 25% of their marrow bearing areas, therapeutic warfarin treatment, and bevacizumab within 12 weeks of enrollment or signs and/or symptoms of bowel obstruction were excluded. Patients provided written informed consent consistent with federal, state, and local institutional review board guidelines at each participating GOG institution in accordance with assurances filed with and approved by the Department of Health and Human Services.

Treatment Plan and Dose Modifications

The initial dose of motesanib (Amgen, Thousand Oaks, CA) was a fixed oral daily dose of 125 mg until disease progression or adverse effects prohibited further therapy with this agent. Caution was recommended for patients taking CYP3A4 substrates, such as ketoconazole, that have a narrow therapeutic index. A cycle equaled 28 days. Motesanib was supplied by Amgen.

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 3.0. For first occurrence of febrile neutropenia and/or documented grade 4 neutropenia, motesanib was held until the absolute neutrophil count (ANC) was grade ≤ 2 and then reduced to 100 mg daily. Treatment was held for occurrence of grade 4 thrombocytopenia in patients until they recovered to grade ≤ 1 and then were reduced to 100 mg daily. The next cycle of motesanib did not begin until the ANC was ≥ 1500/μL and the platelet count was ≥

100,000/μL. Therapy could be delayed up to a maximum of two weeks. Patients who failed to recover adequate counts within this time period were removed from study treatment. Prophylactic use of myeloid growth factors was prohibited. A second dose reduction to 75 mg orally once a day was also allowed. If toxicity recurred to grade 2 or worse at the 75 mg daily dose, the patient would be discontinued from study drug. Patients who experienced grade 2 or worse non-hematologic toxicity had therapy held until resolution to grade 1 or better up to a maximum of 14 days. Motesanib was then restarted at a one dose level reduction. Exceptions to the above modifications include: liver function tests were required to be grade 3 or worse toxicity before dose modification was required; there was no dose adjustment for fatigue or alopecia. Doses were reduced only for grade 3 gastrointestinal toxicities that could not be controlled with medical management. Once a patient's dose was reduced, no subsequent increases were permitted.

Response Assessment

Patients were evaluated clinically every four weeks and radiographically every eight weeks. The same evaluation modality was used throughout for each patient on study. Response criteria used were as defined by RECIST [17].

Translational Research (TR)

Detailed methodology and references for isolating and phenotyping circulating tumor cells (CTC) and circulating endothelial cells/ circulating endothelial progenitors (CEC/CEP) can be found in the published online only supplemental material. The methodologies and references for VEGF determination by ELISA and extraction and quantification of total plasma cell-free DNA (cfDNA) are also found in supplemental material.

Statistical Methods

The potential activity of the drug was to be evaluated with the co-primary endpoints of tumor response and survival without progression for 6 months (6 month PFS), using the method of Sill et al [18]. Uninteresting, null probabilities were determined from historical controls which are listed in Usha et al and found to be 10% and 15% for response and 6 month PFS, respectively [19]. The 2-stage design targeted about 26 patients in each stage in order to enable the study to stop early for futility and detect 15% and 20% increases in the probability of response or 6 month PFS with 90% power at the 10% level of significance. Secondary endpoints included overall survival (OS), PFS, and adverse events deemed at least possibly related to treatment. Since the study was terminated for potentially treatment related adverse events, patients could not be reliably characterized on measures of treatment efficacy, so with the exception of OS, these statistics were not calculated or are presented with caution. All TR excluded associations with patient outcomes related to treatment efficacy (PFS, OS, and response). Instead, associations between biomarkers and with demographic qualities including platinum sensitivity, performance status, number of prior regimens, grade of tumor, and age were examined with Spearman's correlation [20]. Estimates of the median change in biomarker values along with 95% confidence intervals (CI) were provided for the sample that submitted post-treatment tissue. Estimates of the Hodges and Lehmann shift parameter along with 95% CI, which are associated with Wilcoxon's rank sum test, were provided for biomarkers across the demographic variables listed above [21,22]. These exploratory analyses were hypothesis generating so that p-values<0.05 were deemed suggestive and worthy of further examination (p-values between 0.05 and 0.1 suggested a trend).

RESULTS

Patients

Twenty-three patients were enrolled onto the trial. One patient was deemed ineligible due to improper pre-protocol treatment. Patient characteristics are listed in Table 1. All but one patient had a performance status of 0 or 1. The median age was 64.5 years (range, 50-82 years). Nineteen of 22 patients had ovarian cancer with the remainder divided between fallopian tube or primary peritoneal carcinoma. Approximately 68% of the patients had received two prior regimens.

Toxicity

Enrollment to the trial was halted after four patients developed posterior reversible encephalopathy syndrome (PRES) with symptoms including aphasia and seizures. There were three cases reported in the initial 20 patients treated. It then was decided by the GOG and Amgen that only normotensive patients not requiring medication should be enrolled. One more patient developing PRES would then close the trial. A fourth patient developed PRES causing the GOG to close the trial immediately and stop study treatment for all patients enrolled on the study. Symptoms included grade 3 or 4 confusion and seizures (Table 2). MRI studies initially were consistent with that of a cerebrovascular accident (CVA), but all symptoms and radiographic findings resolved within 3-7 days of presentation. Grade 3 hypertension was observed in two patients with PRES with one additional patient with PRES having grade 1 hypertension. All three of these patients had baseline blood pressures of 130-140/70-80. The protocol called for blood pressure monitoring weekly for the first six weeks and then prior to each cycle as a minimum with more intensive monitoring left up to treating physicians. All of the PRES episodes occurred within the first 10 days. Other grade 3 toxicities included diarrhea, cholecystitis, hypocalcemia, hypophosphatemia and nonspecific pain. All four patients who developed significant neurological toxicity had serous histology. No obvious renal toxicity was observed. Grade 1 headache occurred in three of the four patients that developed PRES. There were no reported visual disturbances.

Efficacy

It is difficult to assess the efficacy of motesanib in ovarian cancer from this study as patients still were receiving study therapy when the trial was closed. The estimate of the proportion responding is likely negatively biased. One patient did have a partial response, seven patients had stable disease at the time when most were removed from study treatment (one patient was removed after cycle 2, four patients were removed after cycle 3, two patients were removed after cycle 4, and one stable disease patient refused further therapy during cycle 2), and two had progressive disease. Twelve of the 22 evaluable patients (55%) had indeterminate response when the trial was prematurely closed secondary to the neurological events previously described (Table 3). Overall, 16 of the 22 patients were removed from study before progression of disease or toxicity developed. Six patients were withdrawn from study for reasons related to toxicity or progression. Four patients were withdrawn from the trial due to toxicity (PRES), one patient refused further therapy (perhaps due to diarrhea), and one patient had progressive disease. A patient with progressive disease was evaluated about a week after study withdrawal. Overall, the distribution of cycles of therapy were 7 with one cycle of therapy, 9 with two cycles, 4 received three cycles, and 2 had four cycles.

Translational Research

CTCs and CECs/CEPs - CTCs were detected in four of 22 patients, two of whom had CTC at baseline (CTC=1 and 23 per 4mL). The limited number of patients with CTC at baseline

did not allow statistical comparisons to previous findings in this patient population. M30 analysis, intended for use as an apoptotic biomarker, was not possible due to the low number of patients with detected CTCs. Table 4 shows the median number of CD34+/CD146+ CECs, % CD133+ CEPs, and % VEGFR+ CECs per 4mL at each time point. Changes in CECs/CEPs between cycles 1 to 2 were not associated with demographic characteristics.

VEGF ELISA

Table 5 shows the median levels of VEGF at each time point. Plasma levels of VEGF were not associated with patient characteristics and did not decrease over time. However, there was a suggested decrease in VEGFR from cycle 1 to cycle 2 (median ratio was 0.127; 95% CI 0.071-0.515; n=11).

Cell Free DNA

Table 6 shows the median genome equivalents/ mL (GE/mL) of each housekeeping gene analyzed at the three time points. Concentrations of cell free DNA were not associated with patient characteristics.

DISCUSSION

It is not possible to reliably evaluate the activity of motesanib in patients with recurrent ovarian cancer from this trial as a vast majority of patients had study drug withdrawn prior to any response evaluation due to the significant central nervous system (CNS) toxicity observed in four patients. Posterior reversible leukoencephalopathy has been seen with other antiangiogenic agents as well as other classes of drugs, such as immunosuppressants. It was first reported by Hinchey and colleagues in 1996 [23]. Key symptoms include headache, seizures, altered mental status, and loss of vision. Imaging studies of the brain are consistent with a posterior leukoencephalopathy, i.e., extensive bilateral white matter abnormalities suggestive of edema in the posterior regions of the cerebral hemispheres. In the initial report, 12 of 15 patients had an abrupt increase in blood pressure and had some impairment of renal function. In our series, the majority of patients who developed PRES developed hypertension, but none of our patients had any renal dysfunction. Such changes may also have been seen in other cerebral regions, such as the brain stem or the cerebellum. All signs and symptoms resolved within two weeks. Common precipitants of PRES are acute elevations in blood pressure, renal decompensation, fluid retention, e.g., eclampsia, treatment with immunosuppressive drugs and now antiangiogenic agents [24- 32]

While the etiology of PRES remains poorly defined, one commonly postulated mechanism is that it is due to sudden elevations in systolic blood pressure that exceed the auto regulatory capacity of the posterior vasculature of the brain where there is a relative lack of sympathetic innervation 24,25]. Subsequent hyperperfusion ensues with protein and fluid extravasation leading to vasogenic edema. An alternative mechanism implicates direct endothelial damage or vasospasm with subsequent ischemia. Precipitating pathology may include directly toxic effects of these drugs on vascular endothelial cells. There may be release of endothelin, prostaglandin, and thromboxane A2 versus direct endothelial damage through the release of these mediators. Endothelin is a potent vasoconstrictor while the other two mediators can cause microthrombi, all of which can lead to cerebral capillary leak. Thrombotic microangiopathy (TM) is a known consequence of bevacizumab and sunitinib therapy [31,32]. The absence of clinical or biological signs and symptoms does not eliminate the possibility of TM as an underlying cause of the neurologic toxicities observed with motesanib in this trial or in several other patients receiving this drug in other trials [33]. A recently published case report describes a patient with renal cell carcinoma treated with bevacizumab who acutely developed severe hypertension, nephrotic syndrome, and renal

failure with evidence of a hemolytic uremic syndrome (HUS)[31]. Renal biopsy of this patient revealed thrombotic microangiopathy. Podocyte lesions contained VEGF as detected by immunohistochemical staining. Symptoms abated with stopping bevacizumab therapy. The patient was treated two months later with sunitinib with recurrence of symptoms and findings consistent with HUS. Symptoms reversed after cessation of the new drug and plasma exchange. A more recent case report describes a patient with GIST treated with sunitinib who developed hypertension, TM, and PRES [33]. Laboratory studies were consistent with a thrombotic thrombocytopenia purpura (TTP)-like picture with an MRI of the brain showing findings consistent with PRES. This mechanism is less likely to be operative in the patients in this series since no changes in renal function were noted; however, no renal biopsies were performed in the absence of any clinical pathology.

It is known that certain drugs such as ketoconazole are potent CYP3A4 inhibitors. Motesanib is metabolized by this cytochrome [34]. A pharmacokinetic study demonstrated that patients administered ketoconazole while receiving motesanib had an 86% increase in area under the curve from 0-24h ($AUC_{0\text{-}24h}$) and a 35% increase in maximum plasma concentration (Cmax) for motesanib. No PRES was observed, but 21% of the patients experienced grade 3 hypertension. Detailed medication lists are not available for the four patients who developed PRES and no pharmacokinetic sampling was performed for this trial.

Blood was collected from patients prior to cycles 1, 2, and 3 and used to evaluate the number of CTC and CEC/CEP, plasma levels of VEGF and cell-free DNA. CEC enumeration (CD146+CD34+) was determined by the phenotyping of the CD34+-ferrofluid captured population. The use of CECs as surrogate angiogenesis markers has been reported in preclinical studies using murine models of cancer and in several clinical studies of angiogenesis inhibitors [35,]. The CD 34+/146neg population represents hematopoietic stem cells. A decrease in their number with treatment would reflect a lack of bone marrow reserve and could be associated with increased hematologic toxicity. In one study, at least a two-fold increase in mature (CD146+) CECs was seen during the first cycle of therapy (36). These CECs are thought to represent vessel wall-derived endothelial cells damaged or rendered apoptotic in response to therapy. We evaluated whether VEGF level and/or VEGFR status could be an indicator of response to treatment with motesanib. Nine patients had baseline and pre Cycle 2 samples evaluated. Seven of the nine patients did show both a decrease in VEGFR expression and in VEGF plasma levels. The observed Spearman's correlation coefficient was 0.1 (approximate 95% CI -0.66 to 0.85). Statistically, this sample size is underpowered to detect clinically significant associations. A larger sample of patients would be needed to determine whether these parameters could be used to evaluate the activity of an anti-angiogenic therapy.

Pre-clinical studies suggest that tumor-specific cfDNA levels correlate with increasing tumor burden and decline following therapy and tumor-specific DNA may be a useful surrogate biomarker of therapeutic response (37). In this study, there were no statistically significant changes in the three housekeeping genes at three time points, possibly due to early closure and limited sample size. The mechanisms of cfDNA release in blood under normal and pathological conditions are not fully understood. It is thought that cfDNA levels might be influenced by apoptosis, necrosis, decreased DNAase activity in circulating cancer cells, as well as clearance by liver/kidney, and modification status of cf DNA. Whether cfDNA can be used as a predictive marker for anti-angiogenic therapy will need to be validated in larger studies. Motesanib is a multi-tryosine kinase inhibitor. In addition to its other targets, it also inhibits RET 38,39]. VEGF-A, the major isoform of VEGF which is the target for bevacizumab, induces RET phosphorylation and up regulation of glial cell line-derived neurotrophic factor (GDNF) in addition to VEGF-R2 autophosphorylation [40].

VEGF and GDNF (a ligand for RET) have additive effects on RET phosphorylation. GDNF has an important role in promoting normal ovarian follicle development [41]. GDNF is predominantly produced by oocytes rather than somatic cells and mediates auto and paracrine cell-cell interactions required during folliculogenesis in normal ovarian tissue. GDNF also is important in human fetal brain development [42]. As fetal age increases, GDNF expression shifts to neurons and glial cells in deeper structures of the brain. Widespread GDNF expression in neuronal and non-neuronal brain cells with distinct developmental shifts suggests that GDNF has a critical role in survival differentiation and maintenance of neurons at different stages of development in the developing human fetal brain. While it is less clear if GDNF helps maintain the health of the adult brain, RET inhibition in some way may have contributed to the neurotoxicity observed in the four patients who developed PRES in this trial.

Clinical efficacy could not be assessed in this trial to the unexpectedly high incidence of PRES. It is difficult to be enthusiastic about the further development of this compound in the treatment of ovarian cancer in light of its minimal efficacy in larger trials in other disease sites (16) and its significant toxicities.

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RESEARCH HIGHLIGHTS

- Motesanib is a small molecule inhibitor of multiple receptor tyrosine kinases including VEGFR 1-3, c-KIT and PDGFR.
- High incidence (4/23) of posterior reversible encephalopathy syndrome with no clear understanding of underlying etiology.
- The trial was closed early so no conclusions can be drawn regarding its activity in patients with recurrent ovarian cancer.

Table 1

Patient Characteristics (n=22)

Characteristic	Category	No.	%[a]
Age	50-59	7	32
Median 64 years	60-69	9	41
Range (50-82)	70-79	5	23
	80-89	1	5
Race	American Indian	2	9
	White	20	91
Performance Status	0	15	68
	1	6	27
	2	1	5
Site of Disease	Ovary	19	86
	Fallopian tube	1	5
	Primary peritoneal	2	9
Cell Type	Adenocarcinoma, Unsp.	2	9
	Clear Cell Carcinoma	1	5
	Endometrioid Adenocarcinoma	2	9
	Serous Adenocarcinoma	17	77
Grade	2	6	27
	3	16	73
Prior Chemotherapy	1	7	32
	2	15	68
Prior Radiation	No	20	91
	Yes	2	9
Prior Surgery	No	1	5
	Yes	21	96

[a]Some of the % add up to 101% due to rounding off to the nearest whole number.

Table 2

Toxicities Grade 3 or 4 (n=22)

Toxicity	3	4
Hypertension	2	-
Diarrhea	2	-
Cholecystitis	1	-
Metabolic	1	-
Hypocalcemia	1	-
Creatinine	1	-
Neurological	3	1
Confusion	1	-
Seizures	2	1
Pain - Abdomen - NOS[a]	1	-

[a]NOS – not otherwise specified

Table 3

Responses (n=22)

	No.	%[a]
Partial response[a]	1	5
Stable disease	7	32
Progressive disease	2	9
Indeterminate[b]	12[b],	55

[a]% sums to 101% due to rounding of to the nearest whole number.

[b]Seven patients were indeterminate because study treatment was terminated early.

Table 4

CEC/CEP Pre-Cycles 1, 2, and 3

CEC/CEP[a]	Pre-cycle	*N*	Q1	Median	Q3
CD34+/146+	1	18	35	68	91
	2	15	129	180	259
	3	5	113	117	230
% CD133	1	14	0	0	0
	2	12	0	0	0
	3	5	0	0	0
% VEGFR2	1	17	11	19	24
	2	14	2	3	8
	3	5	4	4	6

Q1 = lower quartile, Q3 = upper quartile

[a] = number per 4 mL of blood

Table 5

VEGF Levels in Pre-Cycles 1, 2, and 3 Plasma

	VEGF [pg/mL]			
Pre-cycle	***N***	**Q1**	**Median**	**Q3**
1	20	65	117	221
2	12	45	100	205
3	4	19	54	112

Q1 = lower quartile, Q3 = upper quartile

Table 6

Concentration of Cell Free DNA (Genome Equivalents [GE]/mL) in Pre-Cycles 1, 2, and 3 Plasma

Gene	Pre-cycle	*N*	Q1	Median	Q3
GADPH	1	20	3162	4756	19261
	2	11	3201	6296	14878
	3	4	2513	6770	36347
β-actin	1	20	2605	4318	15676
	2	12	2669	4711	14017
	3	4	3210	5701	26393
β-globin	1	20	2230	2663	8350
	2	12	1141	2876	6826
	3	4	1436	4027	18837

Q1 = lower quartile, Q3 = upper quartile