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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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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.

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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.

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.

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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 $\geq$1,500/μL, platelet count $\geq$100,000/μL), renal (serum creatinine $\leq 1.5\times$ the upper limit of normal), and hepatic function (total bilirubin $\leq 1.5\times$ the upper limit of normal, and transaminases and alkaline phosphatase $\leq 2.5\times$ 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 $\leq$2 and then reduced to 100 mg daily. Treatment was held for occurrence of grade 4 thrombocytopenia in patients until they recovered to grade $\leq$1 and then were reduced to 100 mg daily. The next cycle of motesanib did not begin until the ANC was $\geq$1500/μL and the platelet count was $\geq$100,000/μL. Therapy could be delayed up to a maximum of 2 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 4 weeks and radiographically every 8 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.