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A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer☆

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ABSTRACT

Objective. The progression-free and median survival of patients with advanced ovarian cancer has not appreciably improved over the last decade. Novel targeted therapies, particularly antiangiogenic agents, may potentially improve clinical outcomes in patients with ovarian cancer. This phase II, open-label study evaluated oral pazopanib monotherapy in patients with low-volume recurrent ovarian cancer.

Methods. Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with complete CA-125 response to initial platinum-based chemotherapy and subsequent elevation of CA-125 to ≥42 U/mL (>2×ULN) were treated with pazopanib 800 mg once daily until PD or unacceptable toxicity. This Green–Dahlberg study required 2 CA-125 responses in stage I (20 patients) to proceed to stage II (15 patients). The primary endpoint was CA-125 response (≥50% decrease from baseline, confirmed ≥21 days after initial evaluation).

Results. Eleven of 36 patients (31%) had a CA-125 response to pazopanib, with median time to response of 29 days and median response duration of 113 days. Overall response rate was 18% in patients with measurable disease at baseline. The most common adverse events leading to discontinuation of study drug were grade 3 ALT (8%) and AST (8%) elevation. Only 1 grade 4 toxicity (peripheral edema) was reported.

Conclusions. Pazopanib monotherapy was relatively well tolerated, with toxicity similar to other small-molecule, oral angiogenesis inhibitors, and demonstrated promising single-agent activity in patients with recurrent ovarian cancer. Further studies evaluating the potential role of pazopanib in patients with ovarian cancer are ongoing.

Introduction

Ovarian cancer (OC) is the fourth-leading cause of cancer-related deaths among women [1]. Despite extensive effort and multiple clinical trials evaluating various chemotherapy regimens, there have been no substantive improvements in clinical outcomes for patients with advanced ovarian disease over the last decade [2–4]. Most women present with advanced disease, and undergo optimal debulking surgery followed by 6 to 8 cycles of platinum-based adjuvant chemotherapy [5–7]. Although most patients respond to initial treatment, up to 70% of patients with advanced-stage ovarian or primary peritoneal cancer subsequently relapse [8]. The median time to progression after primary chemotherapy is about 16 to 20 months, and the median overall survival (OS) in patients with advanced OC is 31 to 51 months [3,4,9]. An increase in serum cancer antigen (CA-125) is the first sign of disease recurrence in most patients and commonly precedes symptom onset or radiologic evidence of progressive disease (PD) by a median 4-month lead time [10]. CA-125 is commonly evaluated every 2 to 4 months for the first 2 years after completing chemotherapy and every 3 to 6 months thereafter [7,11], although the need for CA-125 surveillance has recently been challenged.

There are well-established Gynecologic Cancer Intergroup (GCIG) criteria defining CA-125 progression and CA-125 response [12,13]. Retrospective analysis of progression-free survival (PFS) of patients in the experimental arms of the Taxol Intergroup Trial, assessed using either CA-125 doubling or standard Response Evaluation Criteria in

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Solid Tumors (RECIST), yielded similar results, supporting use of CA-125 as a surrogate efficacy endpoint [10]. Accordingly, we elected to evaluate CA-125 response in this study as well as RECIST in patients with measurable disease.

The optimal management of asymptomatic patients with a rising CA-125 is controversial. Evidence from a recently presented clinical trial suggests no benefit from commencing chemotherapy until symptomatic progression [14], and many clinicians withhold chemotherapy until patients develop symptoms, whereas others institute second-line therapy at the time of CA-125 recurrence. Although platinum-based regimens are commonly used at recurrence, clinical benefit is limited by cumulative toxicity and subsequent development of drug resistance [15]. Most patients with rising CA-125 are initially asymptomatic, have a small volume of disease, and are a good population in which to evaluate the activity of novel, targeted therapies.

Multiple lines of evidence suggest that angiogenesis plays a critical role in the growth of ovarian tumors and is therefore a potentially viable therapeutic target [16–18]. For example, several studies have established an inverse correlation between angiogenesis and OS and PFS in women with advanced OC [17,19,20], and preclinical and clinical data show that antibodies targeting vascular endothelial growth factor (VEGF) inhibit ascites formation, a common finding at initial presentation and at relapse that is associated with a poor prognosis [21,22].

Pazopanib (Votrient™, GlaxoSmithKline), approved by the United States Food and Drug Administration in October 2009 for the treatment of patients with advanced renal cell carcinoma [23], is an oral angiogenesis inhibitor targeting VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-Kit [24]. Phase I testing demonstrated a manageable toxicity profile and activity in a range of solid tumors [25]. To assess pazopanib's potential utility as maintenance therapy after chemotherapy, the current study investigated the activity of pazopanib in asymptomatic patients with recurrent OC who had GCIG-defined CA-125 progression and small-volume disease.

Methods

Patients

Eligible patients were ≥21 years of age with histologically or cytologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. All patients had received ≤2 prior treatment regimens, including first-line platinum-based chemotherapy for ovarian disease. Patients who had received prior adjuvant chemotherapy after first-line treatment (including tamoxifen or monoclonal antibody therapies that target CA-125 [e.g., oregovomab] if the CA-125 level was rising) and neoadjuvant therapies (recorded as a single line of therapy, per protocol) were eligible. In addition, patients must have had CA-125 levels ≥42 U/mL after a complete CA-125 response (defined as a normalized CA-125 value [i.e., ≤21 U/mL]) to first-line platinum-based therapy and no evidence of disease or nonbulky disease. Inclusion was restricted to patients with small-volume disease (e.g., minimal ascites not causing abdominal distention/mesenteric thickening or not requiring paracentesis, or lesions ≤4 cm by spiral computed tomography [CT] or magnetic resonance imaging [MRI] at baseline) to minimize the potential for bowel perforations observed in previous trials with angiogenesis inhibitors. Additional eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate bone marrow, renal, and hepatic function.

Patients who had received prior therapy with pazopanib or any other angiogenesis inhibitors; patients who had major surgery, chemotherapy, hormonal therapy, biologic therapy, immunotherapy, or radiotherapy within the preceding 28 days; or patients with a previous diagnosis of leptomeningeal disease, brain metastases, or another malignancy were excluded. Additional exclusion criteria included poorly controlled hypertension; QTc prolongation (i.e., QTc interval >480 ms); previous Class III or IV heart failure; history of cerebrovascular accident within 6 months; history of myocardial infarction, hospitalization for unstable angina, or cardiac angioplasty or stenting within 3 months; untreated venous thrombosis; malabsorption syndrome; or any condition that interfered with oral administration of the study drug.

Study design and treatment

This nonrandomized, open-label, multicenter phase II trial (VEG104450; NCT00281632) had a 2-stage Green-Dahlberg design with a stopping rule to allow early termination for lack of efficacy [26]. An interim efficacy evaluation of 20 patients enrolled in stage I required at least 2 patients to have a CA-125 response as assessed by Rustin criteria [12] for continuation of the study to stage II.

Patients were scheduled to receive daily oral pazopanib 800 mg over 28-day treatment cycles until clinical or radiologic evidence of PD, withdrawal from treatment because of unacceptable toxicity, or withdrawal of consent. In the event of significant hematologic and nonhematologic toxicities, including grade 3/4 anemia, neutropenia, thrombosis, and thrombocytopenia; grade ≥2 coagulopathy, hemorrhage, and hepatobiliary toxicity; hypertension (symptomatic or systolic blood pressure ≥170 mm Hg or diastolic blood pressure ≥110 mm Hg); and proteinuria (24-h urine protein ≥3 g), the dose of pazopanib was reduced to 400 mg and the patient was monitored for 10 to 14 days. If the toxicity did not recur or worsen, the dose was increased to 600 mg with continued monitoring for an additional 10 to 14 days. If adequately tolerated, the standard 800 mg dose was resumed. If treatment was withheld for >21 days, disease assessments (CA-125 and CT scan/MRI, if applicable) were repeated before continuation of treatment. With regard to hepatic toxicity, a more conservative approach was adopted; per protocol amendment, pazopanib was discontinued if alanine aminotransferase or aspartate aminotransferase increased >8 times the upper limit of normal, even with subsequent recovery to normal.

The study protocol and amendments were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board. This study was conducted in accordance with "good clinical practice," all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. All patients provided written informed consent.

Endpoints

The primary objective of this study was to assess the best biochemical response rate (as determined by CA-125 response after daily pazopanib administration, based on modified GCIG criteria) [12,27]. CA-125 response was defined as ≥50% decrease from the baseline CA-125 level and confirmed ≥21 days after initial evaluation (baseline was defined as the higher value of 2 pretreatment CA-125 assessments). The response was further qualified as normalized (if the assessed CA-125 was ≤21 U/mL) or non-normalized. Progressive disease was defined as a CA-125 increase ≥100% from nadir (if nadir >21 U/mL) or ≥42 U/mL (if nadir ≤21 U/mL); nadir was defined as the lowest CA-125 level until current assessment. If PD was not confirmed after 21 days, it was classified as unconfirmed PD. Stable disease (SD) was defined as changes in CA-125 not qualifying as either PD or response.

Secondary objectives included assessment of the overall response and SD rate based on biochemical, radiographic, and physical examination, and PFS. Modified GCIG criteria [12,27] were used to assess overall response in patients with measurable disease, based on the best response from biochemical, radiologic (defined according to RECIST) [28], and physical examinations. Progression-free survival was defined as the interval from the first dose of study drug to the date of documented PD assessed by biochemical, radiological, and clinical assessment, or to date of death by any cause.