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Phase II clinical trial of bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma☆,☆☆,★

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HIGHLIGHTS

► Ab-paclitaxel with bevacizumab demonstrated substantial antitumor activity with response rate of 50% and median PFS of 8.08 months.
► Toxicity profile was manageable with the most common grade 3–4 adverse events including gastrointestinal disorders, neutropenia, and hypertension.

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ABSTRACT

Objective. We examined the safety and efficacy of combining bevacizumab with albumin-bound (ab-) paclitaxel to treat patients with recurrent, platinum-resistant primary epithelial ovarian or peritoneal carcinoma.

Methods. Patients had measurable disease per RECIST guidelines, progressing within 6 months after a prior course of platinum-based treatment. Patients received ab-paclitaxel 100 mg/m^2 given by intravenous infusion over 30 min on days 1, 8, and 15 of a 28-day cycle with bevacizumab 10 mg/kg given on days 1 and 15.

Results. Forty-eight patients with an average 1.8 prior lines of treatment participated. The overall response rate was 50% (24/48) (95% CI, 34.8% – 65.1%), with 4 complete and 20 partial responses. Fourteen patients (29%) had stable disease, whereas eight (17%) had progressive disease, and two (4%) were not evaluable. Patients received a median of 6 treatment cycles (range, 1 – 31 cycles). The median progression-free survival was 8.08 months (95% CI, 5.78 – 10.15 months); 6 month progression-free rate was 62.5% (95% CI, 47.8%–77.2%); median overall survival was 17.15 months (95% CI, 13.57 – 23.82 months). Grade 3–4 adverse events included gastrointestinal disorders (18.8%), neutropenia (8.3%), and hypertension (6.3%).

Conclusions. Ab-paclitaxel with bevacizumab clearly demonstrates antitumor activity and manageable toxicity profile in patients with recurrent, platinum-resistant ovarian carcinoma. This regimen should be evaluated in a larger randomized trial.

Introduction

Epithelial ovarian cancer (EOC) is the most common cause of death from gynecologic tumors in the United States, because minimal symptoms of early disease lead to diagnosis only after the disease has reached an advanced stage (III and IV) [1]. About 1 in 71 women will develop ovarian cancer in her lifetime. The American Cancer Society estimated that there would be 21,990 new cases of ovarian cancer in 2011 and 15,460 deaths [2]. The incidence has been declining by 1.0% per year since 1992 [2].

In advanced disease, treatment typically entails surgery followed by platinum-based chemotherapy. The 5-year survival in patients with advanced disease with distant metastases is 28% [2]. Recurrent

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ovarian cancer is classified into two categories that are dependent upon the length of time the patient remains disease-free after completing standard of care platinum-based chemotherapy: (1) platinum-sensitive: relapse that occurs more than 6 months after initial chemotherapy; (2) platinum-resistant: earlier relapse. Patients with platinum-sensitive disease may exhibit a good response when retreated with a platinum-based regimen [3,4]. Several agents have shown promise for platinum-resistant disease including: liposomal doxorubicin [5], topotecan [6], oral etoposide [7], gemcitabine [8], and docetaxel [9].

There is still a need for innovation in the treatment of platinum-resistant disease, and anti-angiogenic agents offer promise as have regimens with weekly paclitaxel. Angiogenesis is an important factor in development, growth, and metastasis in ovarian cancer [10]. Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA) is a humanized monoclonal antibody with potent anti-angiogenic effects and has been shown to be effective in the treatment of recurrent ovarian cancer, both as a single agent and in combination with other agents [11–19]. The most frequent grade 3–4 toxicity associated with bevacizumab treatment is hypertension [20], but in ovarian cancer specific concerns have been raised about gastrointestinal perforations [21,22].

Recurrent ovarian cancer has also been treated with good response using weekly paclitaxel even in patients previously treated with a taxane [23,24]. The availability of albumin bound (ab-) paclitaxel (Abraxane®, Abraxis BioScience, LLC, Bridgewater, NJ) has made administration of paclitaxel more efficient, and this formulation has shown tolerability in recurrent ovarian cancer patients [25]. Weekly ab-paclitaxel has not been extensively studied in ovarian cancer, but a weekly regimen of ab-paclitaxel identical to the dose used in this study was reported in a Phase II study, and the toxicities at grade 3 or higher were neutropenia, anemia, gastrointestinal, metabolic, pain, leukopenia, and neurosensory toxicity [26].

This Phase II study was conducted to evaluate the safety and efficacy of combination bevacizumab and ab-paclitaxel in the treatment of recurrent, platinum-resistant primary epithelial ovarian cancer and primary peritoneal cancer.

Patients and methods

Patients

Patients were recruited over 24 months from 9 oncology clinics in the United States associated with ACORN Research, LLC (Memphis, TN). All potential patients were approached and given the opportunity to participate. Eligible patients had recurrent or progressive primary EOC or peritoneal carcinoma (PC) within 6 months of their last previous platinum therapy and met the following inclusion criteria: at least one lesion ≥ 1.0 cm by CT or MRI; not previously irradiated; absolute neutrophil count (ANC) > 1500/mL; platelets > 100,000/mL; and hemoglobin > 9.0 g/dL; serum creatinine < 1.5 mg/dL and calculated creatinine clearance > 40 mL/min; serum bilirubin < 1.5 mg/dL; and transaminases < 2.5 times the upper limit of normal. Eligible patients also were: at least 18 years old and provided written informed consent; with Eastern Cooperative Oncology Group (ECOG) Performance Status [27] rating of 0–1; at least 30 days post-surgery; with negative serum pregnancy test and adequate birth control. Patients were excluded if they had: life expectancy < 3 months; previous bevacizumab; history of other invasive malignancy, hypertensive crisis, unstable angina, congestive heart failure, myocardial infarction, stroke or transient ischemic attack, abdominal fistula, perforation, or abscess within 6 months. Patients were also excluded if they had: significant vascular disease; brain metastases; peripheral neuropathy ≥ grade 2; large or small bowel obstruction within 3 months; non-healing wound, ulcer, or fracture; proteinuria; or were currently receiving treatment with full-dose anticoagulant therapy.

Study design

The design of this investigation was a Phase II, multicenter, open-label, and single arm combination treatment. Treatment comprised ab-paclitaxel at 100 mg/m^2 given by intravenous (IV) infusion over 30 min on days 1, 8, and 15 of a 28-day cycle with bevacizumab 10 mg/kg given on days 1 and 15. Each treatment cycle was 28 days. Patients responding or with stable disease were treated until disease progression, intolerable toxicity, patient refusal to continue, or investigator decision to discontinue the patient's treatment.

Bevacizumab initial dose of 10 mg/kg was given by continuous IV infusion over 90 min for the first infusion and 30 min for subsequent infusions. Patients who experienced infusion associated adverse events (AEs) were pre-medicated on subsequent infusions with H1, H2 blockers or dexamethasone as indicated by reaction severity.

Ab-paclitaxel was administered at 100 mg/m^2 over 30 min, and two step dose reductions to 80 mg/m^2 or 65 mg/m^2 were specified as needed for toxicities. Subsequent doses were not given until the ANC was ≥ 1500/mL and the platelet count was ≥ 100,000/mL. Dose reductions were used for grades 3 and 4 thrombocytopenia, and granulocyte colony-stimulating factors (G-CSF) were used for grades 3 and 4 neutropenia.

All study procedures were approved by the Western Institutional Review Board (Olympia, WA) and by local institutional review boards as required. Informed consent was obtained from each patient prior to enrollment.

Study endpoints

The primary and secondary objectives, respectively, were to evaluate the antitumor activity and toxicity profile of ab-paclitaxel with bevacizumab. Antitumor activity was measured by overall response rate (ORR), 6 month progression-free rate, progression-free survival (PFS), and overall survival (OS). Toxicities were recorded from clinical examinations and laboratory values that were graded by reference to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE version 3.0) [28].

Assessments

Patients were assessed for tumor response according to the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines version 1.0 [29]. Radiological tumor measurements were performed locally by a radiologist pretreatment, after every third treatment cycle, and at the end of treatment or time of progression. The study plan identified 6 month progression-free rate as the as the primary endpoint, and the study was powered to detect effects on this endpoint. However, the focus of reporting is on PFS as more descriptive of the study findings. ORR as a secondary endpoint was defined as the combined cases meeting criteria for complete response (CR) or partial response (PR) according to RECIST guidelines. OS was also evaluated. Cancer Antigen 125 level (CA-125) was assessed pretreatment, before each treatment cycle, and at the end of treatment or time of progression.

Patients were evaluated clinically and with standard laboratory tests before treatment commenced and at regular intervals during their participation. Safety evaluations included medical interviews, physical examinations, clinical laboratory measurements performed by local laboratories, and recording of all grades of AEs according to CTCAE version 3.0 [28].

Statistical methods

Statistical power was evaluated for the primary endpoint of 6 month progression-free rate, with power evaluated for a hypothesized rate of 30% against a null hypothesis rate of 15%. The analysis