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Phase II trial of bevacizumab with dose-dense paclitaxel as first-line treatment in patients with advanced ovarian cancer

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HIGHLIGHTS

- Bevacizumab with dose-dense paclitaxel and carboplatin has acceptable toxicity.
- Dose-delay is expected but majority complete therapy without growth factor support.
- Changes in Flt-3L may represent a biomarker to response to therapy.

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ABSTRACT

Objectives. To assess the tolerability and efficacy of bevacizumab with carboplatin and weekly paclitaxel as first-line adjuvant therapy for advanced stage ovarian cancer.

Methods. After IRB approval, this single-institution, phase II study enrolled patients with stage III or IV epithelial ovarian cancer after primary cytoreductive surgery to treatment with carboplatin (AUC 5), weekly paclitaxel (80 mg/m2), and bevacizumab (15 mg/kg) every 3 weeks for at least 6 cycles. The primary endpoint was tolerability of at least 4 cycles of therapy, with a target treatment success rate of >60%. Secondary endpoints included progression-free survival (PFS) and response rate. Plasma biomarkers were analyzed by the multiplex ELISA assays.

Results. Thirty-three patients were enrolled with 30 evaluable patients receiving at least one cycle of combination treatment. Twenty-three patients (77%) were able to complete at least 4 cycles of therapy per protocol, and the posterior probability that the treatment success rate is >60% is 0.77. Twenty-one patients (70%) were able to complete ≥6 cycles of therapy. Median PFS was 22.4 months for patients with optimal (R0) compared to 16.9 months for optimal ≤ 1 cm (HR 1.71, 95% CI 0.58–4.98, $p = 0.33$), and 16.9 months for suboptimal > 1 cm (HR 3.75, 95% CI 1.05–13.34, $p = 0.04$) disease. Increases in mean Flt-3L was significantly higher in responders versus non-responders (83.4 vs. 28 pg/mL, $p = 0.05$).

Conclusions. Adjuvant bevacizumab with dose-dense chemotherapy is associated with acceptable toxicity and a high likelihood of completing 4 cycles of therapy. Dynamic changes in Flt-3L may represent a predictive marker to treatment response.

1. Introduction

In 2017, a projected 22,440 cases of ovarian cancer will be diagnosed in the United States, leading to 14,080 deaths [1]. Due to a paucity of effective screening modalities, most patients are diagnosed at advanced stages. The most widely adopted standard treatment regimen for advanced ovarian cancer includes cytoreductive surgery and tri-weekly carboplatin and paclitaxel chemotherapy [2]. With this treatment regimen, over 50% of patients achieve an initial complete clinical response, however, the majority develop relapsed disease within the first 2 years, with only 10–30% achieving long-term survival [3]. Newer first-line treatment regimens through phase III randomized controlled trials have shown significantly improved initial response rates and prolonged the time to recurrence. These include combination

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intraperitoneal (IP) and intravenous (IV) cisplatin and paclitaxel [4], dose-dense weekly IV paclitaxel and carboplatin [5–6], and combination therapy with the anti-angiogenic monoclonal antibody, bevacizumab [7–8].

Alternative dosing schedules of chemotherapy with weekly paclitaxel and carboplatin have been evaluated as first-line and salvage chemotherapy in patients with ovarian cancer [9–13]. A phase III trial from the Japanese Gynecologic Oncology Group (JGOG 3016) showed that dose-dense paclitaxel and carboplatin significantly improved progression-free survival (PFS) (28.2 vs. 17.5 months; HR 0.76, 95% CI 0.62–0.91; p = 0.004) compared to the conventional regimen given every 21 days. Median overall survival (OS) was also significantly improved (100.5 vs. 62.2 months; HR 0.79, 95% CI 0.63–0.99; p = 0.04) in the dose-dense treatment group. Rates of adverse events were similar in each treatment group, except grade 3 and 4 anemia was higher in the dose-dense group (69% vs. 44%, p < 0.0001). Hematologic toxicity led to discontinuation of therapy in 60% of the dose-dense group compared to 43% on conventional regimen (p = 0.02). Moreover, at least one treatment cycle was delayed in more patients on dose-dense treatment (76% vs. 67%, p = 0.02) [5–6].

Bevacizumab has been studied in many phase I, II, and III clinical trials in primary and recurrent ovarian cancer, due to the significant role that angiogenesis and neovascularization plays in tumor growth, invasion, and metastases [14–15]. The early use of bevacizumab in Gynecologic Oncology Group (GOG)-170D was as a single agent 15 mg/kg every 21 days which led to 40% of patients surviving progression-free for at least 6 months [16]. The combination of bevacizumab with other cytotoxic therapies stems from preclinical models suggesting possible synergistic interaction [17]. It is hypothesized that increased sensitization to apoptosis or reversal of chemotherapeutic drug resistance occurs when VEGF pathway is interrupted [18]. Two large randomized phase III trials, GOG-218 [7] and International Collaboration on Ovarian Neoplasms (ICON)-7 [8], evaluated bevacizumab and tri-weekly carboplatin and paclitaxel followed by single-agent maintenance bevacizumab as front-line treatment for ovarian cancer. Both trials demonstrated a significantly improved PFS with the addition of bevacizumab to front-line therapy followed by maintenance bevacizumab. Similarly, the favorable results with the use of bevacizumab in the recurrent setting have broadened use of this agent in platinum-resistant ovarian cancer [19].

Recent phase II data has supported the use of bevacizumab (7.5 mg/kg) with dose-dense paclitaxel (80 mg/m2) and carboplatin (AUC 6) in stage I-IV ovarian cancer with median PFS of 24 months. With the interest in the use of bevacizumab in the front-line setting and concern for excess hematologic toxicity with weekly paclitaxel, there have been limited reports on the safety and tolerability of using a combination of bevacizumab (15 mg/kg) with dose-dense paclitaxel and carboplatin. We sought to assess the tolerability, efficacy, and response rate of bevacizumab with weekly paclitaxel and carboplatin.

2. Methods

2.1. Patients

After MD Anderson Institutional Review Board approval, this single-institution, single-arm, non-randomized phase II study enrolled patients from April 2010 until October 2013 with stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube carcinoma. All patients must have undergone primary tumor reductive surgery with a maximal effort at debulking. Patients with no gross residual disease (R0) or residual disease of 1 cm or less after primary surgery were defined as "optimal" and >1 cm defined as "suboptimal". Patients undergoing neoadjuvant chemotherapy were excluded. Patients were included if they were enrolled no later than 12 weeks after initial surgery; had measurable or non-measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; normal organ and marrow function as defined per the protocol. All patients signed approved institutional informed consent.

2.2. Treatment

Enrolled patients received intravenous carboplatin (AUC 5) on day 1 and paclitaxel (80 mg/m2) on days 1, 8, and 15 of each cycle. Bevacizumab (15 mg/kg) was given on day 1 of cycles 2 through 6, thus bevacizumab was not given with the first cycle after primary cytoreductive surgery. One cycle of therapy was given every 21 days. Patients were treated for a total of 6 cycles. The dose of carboplatin at an AUC 5 was chosen given the previous hematologic toxicity reported in JGOG 3016 [5]. Changes to the chemotherapy regimen in patients found to have persistent disease after 6 cycles of protocol-directed therapy or maintenance chemotherapy was made at the discretion of the treating physician.

2.3. Toxicity

Toxicity was monitored before each treatment cycle, with adverse events defined and graded according to Common Terminology Criteria for Adverse Events (version-4). Treatment with bevacizumab, carboplatin, and paclitaxel on day 1 of each cycle was not given unless the absolute neutrophil count (ANC) was ≥1500 cells/mm^3 and the platelet count was ≥100,000/μl. Treatment with weekly paclitaxel on day 8 and 15 of each cycle was not given unless the ANC was ≥1000 cells/mm^3 and the platelet count is ≥75,000/μl. Therapy was delayed for a maximum of 3 weeks until these values were achieved. Patients who failed to recover adequate counts within a 3 week delay were removed from the study. Patients did not receive prophylactic growth factors (filgrastim [GCSF], sargramostim [GM-CSF]) unless they experienced recurrent neutropenic complications after specified treatment modifications. Patients were not eligible to receive PEG-filgrastim on study due to the weekly dosing schedule of paclitaxel. If required, growth factor support was initiated the day after the last dose of chemotherapy and continued until the ANC is sustained 1000 cells/mm^3. For the first occurrence of febrile neutropenia and/or documented grade 4 neutropenia persisting ≥7 days, growth factors (G-CSF) were added at a dose of 5 μg/kg/day (or equivalent dose of sargramostim) given subcutaneously starting the day after the last dose of chemotherapy and continuing through hematopoietic recovery. Dose modifications for the management of hematologic toxicity were applicable to carboplatin and were allowed for paclitaxel non-hematologic toxicities per protocol. No dose reductions were allowed for bevacizumab dosing. If adverse events occurred that required holding the bevacizumab, then the dose remained the same once treatment resumed. If unmanageable toxicity occurred at any time during the study, treatment with bevacizumab was discontinued.

2.4. Evaluation criteria

A CT scan or MRI of at least the abdomen and pelvis was required to establish post-surgical baseline for the extent of residual disease within 4 weeks of start of chemotherapy. Patients considered "suboptimal" received radiographic disease assessment after completion of 3 cycles of study therapy and within 4 weeks after completion of protocol directed chemotherapy. Patients considered "optimal" received radiographic disease assessment after completion of protocol directed chemotherapy. All patients could receive radiographic disease assessment as clinically indicated for suspicion of progressive disease. All patients that had measurable or non-measurable disease were evaluated for clinical efficacy using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1 [20]. Target lesions were to be ≥1 cm in longest diameter by computed tomography or magnetic resonance imaging, ≥2 cm by chest X-ray, or ≥1 cm by physical exam using calipers, except lymph nodes, which were to be ≥1.5 cm on short axis [21]. All

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