

Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer

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Received 11 June 2008
Available online 30 September 2008

Abstract

Objective. To describe the response rate (RR), progression-free survival (PFS), and toxicity profile of combination gemcitabine, platinum, and bevacizumab (GPB) for the treatment of recurrent epithelial ovarian cancer (EOC).

Methods. A chart review of all patients with recurrent EOC who were treated with D1, D15 GPB in a 28-day cycle at a single institution was performed. Standard doses were gemcitabine 1000 mg/m², cisplatin 30 mg/m² or carboplatin AUC 3, and bevacizumab 10 mg/kg. All patients were analyzed for toxicity. RR and PFS were assessed in all patients who received at least 2 cycles of GPB.

Results. Thirty-five patients were identified, and 33 received at least 2 cycles of GPB. The majority of patients (80%) were platinum sensitive. Patients received a median of 6 cycles of GPB (range 1–24). Sixteen patients (48%) had a complete response (CR), and 10 patients (30%) had a partial response (PR), for a total RR of 78%. An additional 5 patients (15%) had stable disease, and only 2 (6%) patients had progressive disease. The median overall PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months (2–22). Two patients (6%) had bowel perforations, and both survived. Hematologic toxicities were most common, with 29% and 14% of patients experiencing grade 3 or 4 neutropenia and thrombocytopenia respectively.

Conclusions. The combination of GPB demonstrated excellent efficacy for the treatment of recurrent EOC. However, serious toxicities occurred, and the safety profile of this combination requires further study.

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Keywords: Gemcitabine; Bevacizumab; Platinum; Recurrent epithelial ovarian cancer; Bevacizumab; Bowel perforation

Introduction

Ovarian cancer is the fourth leading cause of cancer death among women in the United States [1]. Every year about 22,000 women are diagnosed with ovarian cancer and approximately 15,000 women will die from the disease [2]. Although about 75% of patients with EOC will respond to first-line chemotherapy with platinum and paclitaxel, most patients with advanced stage EOC will recur. However, there are multiple active chemotherapeutic agents for the treatment of recurrent EOC. Because of this, the treatment of recurrent EOC can persist for many years. While chemotherapy in the recurrent setting is not

curative, the goal of therapy is to improve quality of life and possibly extend quantity of life while minimizing side effects [3].

Preclinical trials demonstrate synergism between platinum agents and gemcitabine, and gemcitabine may overcome platinum resistance [4,5]. Pfisterer et al. demonstrated that gemcitabine plus carboplatin improves PFS with acceptable toxicity compared to single-agent carboplatin in a randomized phase III trial (median PFS 8.6 months versus 5.8 months) [6]. RR of 16–64% have been achieved with combination gemcitabine plus platinum [5–9].

Angiogenesis is necessary for tumor growth and progression [10]. Angiogenesis is regulated by both positive and negative factors, the most potent of which is vascular endothelial growth factor (VEGF) [11]. Multiple reports have shown that angiogenesis, as measured by microvessel density, is associated with worse survival for ovarian cancer patients [12–16].

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Bevacizumab is a recombinant monoclonal antibody against VEGF, and prevents angiogenesis in animal models [17–19]. As such, it has a different mechanism of action than traditional chemotherapeutic agents. Bevacizumab has been studied extensively in patients with a variety of tumor types, including colorectal, breast, lung, and renal carcinoma [20,21]. Bevacizumab has previously been combined with other multi-drug regimens, such as 5-fluorouracil/irinotecan/leucovorin for metastatic colon cancer with significantly improved survival [22]. The addition of bevacizumab to gemcitabine and carboplatin for the treatment of non-small cell lung cancer was shown to significantly improve PFS as well as RR [23].

Recent reports have demonstrated bevacizumab is active in patients with recurrent EOC. RR of 16–21% have been reported for single-agent bevacizumab for the treatment of persistent or recurrent EOC [24–26]. A recently published phase II trial of bevacizumab with oral cyclophosphamide demonstrated a RR of 24% in patients with recurrent EOC [27]. Wright et al. reported a RR of 35% for bevacizumab in combination with a cytotoxic agent in platinum-refractory EOC patients [28]. In addition, bevacizumab in combination with taxane chemotherapy improves symptoms in patients with refractory EOC [29]. Thus, bevacizumab is an attractive candidate to add to cytotoxic chemotherapy regimens and is currently being investigated in randomized clinical trials as first-line treatment (GOG 218 and ICON 7). The objective of this study is to describe the RR, PFS, and toxicity profile of combination GPB for the treatment of recurrent EOC.

Materials and methods

A retrospective chart review was performed of all patients who initiated treatment with combination GPB (cisplatin or carboplatin) for recurrent EOC between October 2005 (the first time this regimen was used at our institution) and July 2007 at a single institution. Follow-up continued until March 2008. Institutional review board approval was obtained. Patients were identified by reviewing chemotherapy log books. Both platinum sensitive (recurrence > 6 months after completing platinum-based chemotherapy) and platinum-resistant (recurrence < 6 months after completing platinum-based chemotherapy) patients were included. Charts were abstracted for pertinent demographic information, as well as toxicities and treatment response. All patients were included in the toxicity analysis. RR and PFS were calculated for patients who received at least 2 cycles of this combination treatment.

The standard treatment dose was gemcitabine 1000 mg/m², bevacizumab 10 mg/m², and either carboplatin area under the curve (AUC) 3 mg/ml/min or cisplatin 30 mg/m² on days 1 and 15 in a 28-day cycle. The creatinine clearance for calculation of the carboplatin dose was calculated according to the Jelliffe method. Patients were pre-medicated with ondansetron, dexamethasone, and lorazepam, and metoclopramide, dexamethasone, and ativan were given to prevent delayed emesis. The use of granulocyte-colony stimulating factors (G-CSF) and erythropoietin stimulating agents (ESAs) was per physician discretion.

Measurable disease was defined as at least one lesion that was greater than 1cm on spiral CT, as defined by Response to

Treatment in Solid Tumors (RECIST) criteria [30]. In the absence of measurable disease, CA-125 levels were used to assess response per modified Rustin criteria [31]. Complete response was disappearance of gross evidence of disease, resolution of measurable disease on CT scan, or a normalization of CA-125 levels from an elevated level. Partial response was a 30% or greater reduction in measurement of longest dimension of each lesion, or >50% decrease in CA-125 levels. Progressive disease was a 20% or greater increase in measurement of longest dimension of each lesion or the appearance of any new lesion, or a doubling of CA-125 levels within 8 weeks of the start of chemotherapy. Stable disease was any condition which did not meet the above criteria. Best response was reported. CA-125 levels were routinely drawn with the standard pre-chemotherapy labs. CT scans were obtained as appropriate to follow measurable disease and at the physician's discretion. The NCI CTCAE Version 3.0 was used to evaluate toxicities. The worst grade toxicity in each category per patient was reported. PFS is the time from the date of first treatment with combination gemcitabine, platinum, and bevacizumab until disease progression or date of last contact.

Statistical analysis

Simple descriptive statistics were used to report response rates and frequency and severity of toxicities, including percentages, 95% confidence intervals, means, and medians as appropriate. Chi-square was used to calculate differences in proportions. Overall PFS was determined using the Kaplan Meier survival curve. Stata release 10 (College Station, Texas) was used to perform statistical calculations.

Results

Thirty-five subjects were identified, and all were included in the toxicity analysis. Seventeen of these patients are part of an ongoing prospective phase II trial of gemcitabine, carboplatin, and bevacizumab for the treatment of recurrent ovarian cancer. Ninety-four percent (33/35) of the subjects received at least 2 cycles and were analyzed for RR and PFS. The median age was 60 years, and the majority of the subjects were Caucasian. Eighty percent (28/35) of the patients were primarily platinum sensitive. Of these, 21% (6/28) had developed secondary platinum resistance (Table 1).

Patients had received a median of 2 prior chemotherapy regimens (range 1–11). All patients had been treated with platinum-based first-line chemotherapy. The median platinum-free interval was 13 months (range 0–50 months). Seven patients (20%) had received combination gemcitabine and platinum previously. Bevacizumab was added to combination gemcitabine and cisplatin after 4 cycles in 1 patient, and after 5 cycles in another. Seven patients (20%) had been treated with bevacizumab in the past. No patients were treated with combination GPB prior to this study.

Of the 33 patients analyzed for response and PFS, 21 patients received carboplatin while 12 patients were treated with cisplatin combined with gemcitabine and bevacizumab. Two patients had cisplatin substituted for carboplatin due to persistent neutropenia

Table 1

Baseline demographics (N=35)	Number (%) ^a
Median age (range), years	60 (41–77)
Race	
Caucasian	30 (86)
African-American	3 (9)
Unknown	2 (6)
Stage at diagnosis	
I	3 (9)
II	4 (11)
III	25 (71)
IV	2 (6)
Not staged	1 (3)
Histology	
Serous	24 (69)
Endometrioid	3 (9)
Mixed epithelial	3 (9)
Clear cell	1 (3)
Transitional	1 (3)
Unknown	3 (9)
Grade at diagnosis	
1	2 (6)
2	3 (9)
3	28 (80)
Unknown	2 (6)
Residual disease at primary surgery	
No gross residual	13 ^b (37)
Optimal (<1 cm)	20 (57)
Suboptimal (>1 cm)	1 (3)
Unknown	1 (3)
Platinum response	
Sensitive	28 (80)
Resistant/refractory	7 (20)
Secondary resistant	6
Measurable disease	20 (61)
Median platinum-free interval (range), months	13 (0–50)
Median number of previous chemotherapeutic regimens	2 (1–11)

^a Percentages may not add up to 100% due to rounding.

^b One patient received 4 cycles of neoadjuvant chemotherapy.

in one case and thrombocytopenia in the second case. There were several deviations from the standard regimen. The carboplatin doses ranged from AUC 2.5–3, cisplatin 25–30 mg/m², gemcitabine 600–1000 mg/m², and 1 patient was treated with bevacizumab 5 mg/kg. One patient was started on a 21 day cycle (omitting day 15), and three patients were changed to gemcitabine, platinum, and bevacizumab every 21 days for recurrent cycle delays. Eleven patients had the dose of gemcitabine reduced, usually by 20%.

Patients received a median of 6 cycles of combination GPB (range 1–24). Nineteen of the 35 patients (54%) experienced treatment delays. Ten percent (4/482) of treatments were delayed for a median of 1 week (range 1–8 weeks). Treatment delay was more common for patients who received carboplatin in addition to gemcitabine and bevacizumab, as compared to patients who received cisplatin. 36% (5/14) of the patients who were treated with cisplatin were delayed, versus 74% (17/23) of the patients treated with carboplatin ($p=0.05$). The most common reason for treatment delay was thrombocytopenia (cisplatin and carboplatin), followed by neutropenia (carboplatin). Sixteen patients (46%) received G-CSF, and 22 (63%) received erythropoiesis stimulating agents.

Response data (Table 2)

Twenty patients (61%) had measurable disease, while the other 13 patients were followed with CA-125 levels only for response (Table 2). Forty-eight percent (16/33) of patients had a CR (95% CI 31 to 66%), and 30% (10/33) had a PR (95% CI 16 to 49%), for a total RR of 78% (95% CI 61 to 91%). In addition, 5 patients (15%) had stable disease, and only 2 patients (6%) had progressive disease. Ninety percent (19/21) of the patients who were platinum sensitive at the time of treatment with this combination had either a CR or PR, and none had progressive disease. Sixty-seven percent (4/6) of the patients who had developed secondary platinum resistance prior to this treatment responded, and only 1 patient progressed. Of the 6 patients who were primarily platinum-resistant/refractory and evaluable for response, there were 2 (33%) complete responders and 1 (17%) partial responder (see Table 3). Seventy percent of patients with measurable disease were responders (8 CR and 6 PR), compared to 93% of patients followed with CA-125 levels for best response (8 CR and 4 PR). Both patients with progressive disease had measurable disease.

The median overall PFS was 12 months (95% CI 7–15 months), with a median follow-up time of 15 months (range 6–26 months) (see Fig. 1). One patient was lost to follow-up after 7 cycles with stable disease. Two patients were still undergoing treatment with combination GPB at the end of this study. Ten (30%) patients had combination GPB discontinued due to complete CR. Eight patients had this treatment stopped due to progressive disease. Treatment with this combination was stopped in 14 patients due to side effects, 6 who had no evidence of disease, and 8 who had evidence of disease. At last follow-up, 10 subjects had died of disease, 19 subjects were alive with disease, and 6 subjects had no evidence of disease.

Toxicity data (Table 3)

The most common Grade 3 and 4 toxicities were hematologic. Twenty-nine percent (10/35) of subjects had Grade 3 or 4 neutropenia. Grade 3 and 4 anemia occurred in 11% (4/35) and thrombocytopenia in 14% (5/35) of subjects. Grade 3 and 4 non-hematologic toxicities were uncommon (<10%). However, 2 patients (one with no history of hypertension) developed malignant hypertension requiring hospitalization. Carboplatin was discontinued in 3 patients for hypersensitivity reactions, and cisplatin in 1 patient for a reaction. While three patients had grade

Table 2

Response data (N=33)	Number (%) ^a			
Platinum sensitivity	CR	PR	Stable	Progressive
Platinum-sensitive ^b	13 (61)	6 (29)	2 (10)	0
Secondary platinum-resistant	1 (17)	3 (50)	1 (17)	1 (17)
Platinum-resistant/refractory	2 (33)	1 (17)	2 (33)	1 (17)
Total	16 (48)	10 (30)	5 (15)	2 (6)

^a Percentages may not add to 100 due to rounding.

^b Platinum sensitive at time of treatment with gemcitabine, platinum, and bevacizumab.

3 neuropathies, 1 of these was a pre-existing grade 3 neuropathy, and 1 occurred in a patient with a pre-existing grade 2 neuropathy. In total, sixteen patients (46%) had pre-existing neuropathy from previous chemotherapy, the majority (56%) of which was grade 2.

Thirteen subjects were hospitalized for a total of 17 hospital stays during treatment with this combination therapy. Reasons for hospitalization were as follows: placement of VP shunt (unrelated to chemotherapy), anti-coagulation for deep venous thrombosis, failure to thrive, dehydration due to diarrhea, malignant hypertension, hypercalcemia secondary to bone metastases, hyponatremia, fever (no identified source), rectal bleeding, small bowel obstruction, carboplatin administration for hypersensitivity, streptococcal bacteremia, enterovaginal fistula, and bowel perforation.

There were 3 serious gastrointestinal complications. Two patients were diagnosed with bowel perforation, and 1 patient developed an enterovaginal fistula while on treatment. The first bowel perforation occurred after cycle #2 in a platinum sensitive patient who had a CR. An abdominal CT scan revealed an anastomotic leak from the site of her ileo-cecal anastomosis which was performed 15 months prior, with an associated abscess. Of note, the patient had only received one previous chemotherapy regimen. The second bowel perforation occurred after 5 cycles of triple combination chemotherapy in a platinum sensitive subject with a CR. This patient had no prior history of bowel surgery, and had received 2 previous chemotherapy regimens. She was diagnosed with a perforated diverticular

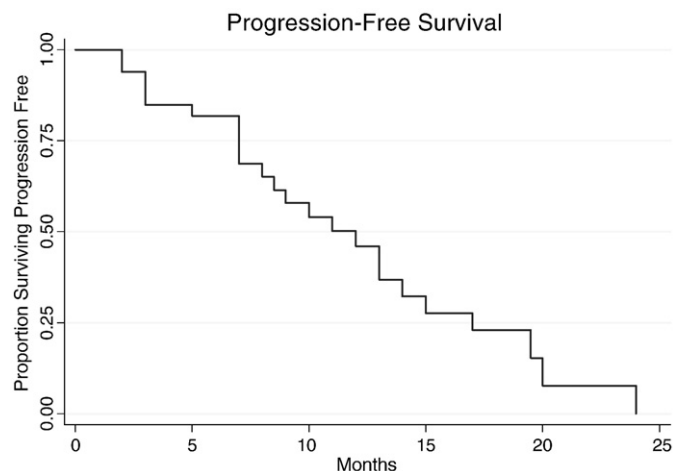


Fig. 1. Kaplan–Meier curve for time to progression. Median PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months.

abscess. The enterovaginal fistula occurred after 3 cycles of GPB in a patient with stable disease.

There was one death while on treatment with combination GPB (cisplatin). This 52 year old patient with a history of well-controlled hypertension and lupus had received 7 cycles of GPB when she was hospitalized for work-up and treatment of hypercalcemia. The patient was noted to have progressive disease, including bone metastases with spinal cord compression. She underwent a neurosurgical procedure for management of the spinal cord compression and spine stabilization, and had a massive cerebrovascular accident on post-operative day (POD) #11. After discussion with the family, the patient was changed to comfort care status and expired POD #14.

Discussion

The combination of GPB is highly active in the treatment of recurrent EOC, with a RR of 78% and a median PFS of 12 months. While single-agent bevacizumab has demonstrated modest activity (RR 16–21%) in patients with platinum-resistant/refractory disease, the addition of bevacizumab to cytotoxics has resulted in a reported RR of 35% [24–26,28]. The higher RR in this study compared to previously published studies incorporating bevacizumab may be attributable to the inclusion of platinum sensitive patients, although the CR in 2 platinum-resistant patients is noteworthy. The RR in this study compares favorably to published RR (16–64%) for combination gemcitabine and platinum, with a longer PFS in the present study [5–9]. The low rate of progressive disease is notable, as 20% of patients had received combination gemcitabine and platinum previously and 20% had been treated with bevacizumab in the past.

While the RR and duration of response are promising, significant toxicities were noted. The occurrence of bowel perforations in ovarian cancer patients treated with bevacizumab has been reported to be 0–15% [24–29,32]. In fact, a phase II trial of bevacizumab in platinum-resistant EOC patients was halted early because of a higher than expected gastrointestinal perforation rate [25]. A recent paper suggested that careful

Table 3
Toxicity data

	Patients, <i>N</i> (%)			<i>(N=35)</i>	
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	9 (26)	11 (31)	7 (20)	0	0
Neutropenia	5 (14)	8 (23)	8 (23)	2 (6)	0
Anemia	10 (29)	14 (40)	4 (11)	0	0
Thrombocytopenia	11 (31)	7 (20)	4 (11)	1 (3)	0
Fatigue	8 (23)	20 (57)	3 (9)	0	0
Pain	4 (11)	10 (29)	3 (9)	0	0
Headache	3 (9)	0	0	0	0
Constipation	16 (46)	2 (6)	0	0	0
Diarrhea	4 (11)	1 (3)	1 (3)	0	0
Nausea	10 (29)	6 (17)	3 (9)	0	0
Fistula, enterovaginal	0	0	1 (3)	0	0
Perforation, GI	0	0	2 (6)	0	0
Neuropathy					
Cranial	0	1 (3)	0	0	0
Sensory	7 (20)	15 (43)	3 (9)	0	0
Creatinine	1 (3)	1 (3)	0	0	0
Proteinuria	4 (11)	10 (29)	0	0	0
Hemorrhage	6 (17)	3 (9)	0	0	0
Thromboembolic	0	0	1 (3)	0	0
Hypertension	1 (3)	3 (9)	1 (3)	2 (6)	0
Liver function tests	4 (11)	1 (3)	0	0	0
Dyspnea	0	2 (6)	0	0	0
CNS ischemia	–	0	1 (3)	0	1 (3)
Allergy	1 (3)	2 (6)	3 (9)	0	0
Mucositis	4 (11)	1 (3)	0	0	0
Rash	0	1 (3)	0	0	0

patient selection may reduce the risk of bowel perforation, by avoiding bevacizumab in patients with clinical symptoms of bowel obstruction, pelvic exam consistent with rectosigmoid involvement, or bowel involvement on CT scan [33]. However, these risk factors were not present in our 2 patients who developed gastrointestinal perforation. Wright et al. suggest that bevacizumab should be incorporated earlier in treatment, as the 2 patients in their paper who suffered from bowel perforation were heavily pretreated [34]. Our patients who experienced gastrointestinal perforation were not heavily pretreated, having received 1 and 2 prior chemotherapy regimens respectively. In addition to bowel perforations, there have been 4 reported fistulas in EOC patients treated with bevacizumab. Further study is required to understand the mechanisms underlying bowel perforation and fistula formation in EOC patients treated with bevacizumab, and to determine if this complication is avoidable by patient selection.

Hematologic toxicities are common when gemcitabine and platinum are combined for the treatment of recurrent EOC. Grade 3 and 4 neutropenia ranges from 28–77% in patients treated with D1, D8 gemcitabine and platinum, depending on the usage of G-CSF support and dose of gemcitabine used [5,6,8,9,35,36]. Oxaliplatin has been combined with gemcitabine in a biweekly treatment schedule, with less hematologic toxicity [37,38]. Bozas et al. demonstrated a significant reduction in grade 3 and 4 neutropenia by using a D1, D15 regimen of combination cisplatin and gemcitabine. The rates of grade 3 and 4 hematologic toxicity in the present study are similar to those reported by Bozas et al [7]. The degree of neuropathy was not surprising, considering almost half of the patients had pre-existing neuropathy. One patient died while on treatment from an arterial thromboembolic event, possibly related to treatment, though the patient had recently undergone a neurosurgical procedure.

There are several limitations to this study. It is retrospective, and therefore subject to the inherent biases of retrospective studies, including selection bias. The treatment doses varied somewhat, but this is probably reflective of real world practice. There is no control group, so the effect that bevacizumab had on the RR cannot be directly measured. The patients were heterogeneous and included platinum sensitive and platinum-resistant patients. Because of the pre-clinical and clinical data suggesting synergism between gemcitabine and platinum, and the high response rates in platinum-resistant patients, we decided to include platinum-resistant patients [4,5,7,8].

In conclusion, combination GPB is highly efficacious in the treatment of recurrent EOC, with an overall response rate of 78%. However, serious adverse events from the addition of bevacizumab to gemcitabine and platinum occurred, especially hypertension and gastrointestinal complications. Currently, the dilemma for the clinician is when to incorporate bevacizumab in the treatment of recurrent EOC. The optimal timing of incorporation of bevacizumab in the treatment of recurrent EOC, the ideal patient, and the appropriate dose is unknown. The risk/benefit profile of the addition of bevacizumab to current cytotoxic regimens has to be carefully weighed. Further studies of the safety profile of this combination are warranted.

In addition, prospective comparisons of combination chemotherapy with and without bevacizumab (GOG 213 and the OCEANS trial) will help to better define the risk/benefit profile of the addition of bevacizumab to cytotoxic chemotherapy for recurrent EOC treatment.

Conflict of interest statement

Some of the patients included in this retrospective study are part of an ongoing prospective phase II trial at The Ohio State University. Funding is provided by Genentech, Inc and Eli Lilly, Corporation. Their funding is evenly distributed by patient enrollment. The funding is not granted until patients are enrolled onto the trial. None of the investigators have any conflicts to disclose.

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