



Prolonged Responses with Bevacizumab-Cyclophosphamide in Patients with Ovarian Cancer: Clinical Experience with 11 Patients



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Abstract

Introduction: Ovarian cancer continues to be one of the most lethal gynaecological cancers. Bevacizumab is effective either as monotherapy or administered in combination with chemotherapy.

Material and methods: This is a retrospective study in patients treated at our institution with bevacizumab-cyclophosphamide, to investigate the efficacy and adverse effects of this treatment modality.

Results: Eleven patients were treated; 54.5% were platinum resistant and 45.5% were platinum sensitive. A median of 21 (range 4-50) cycles of bevacizumab were administered. The overall RR was a complete response (CR) in one patient (9%), a partial response (PR) in 3 (27.3%), and stable disease (SD) ≥ 6 months in 3 (27.3%). The median PFS and OS were 10 and 18 months, respectively. The grade 3-4 toxicities included anaemia [1], transient ischaemic attack [1] and hypertension [1]. Only one patient discontinued treatment as a result of toxicity. We found no cases of intestinal perforation or toxicity-related deaths.

Conclusion: In our population of heavily pre-treated patients, bevacizumab in combination with oral cyclophosphamide had significant activity without significant toxicity and with long lasting PFS.

Introduction

Ovarian cancer continues to be one of the most lethal gynaecological cancers. Around 75% of women with epithelial carcinoma are diagnosed in stages III or IV. In the last few years, drugs with antiangiogenic action have been shown to be active in ovarian cancer [1]. Current systemic therapy for advanced ovarian carcinoma consists of a combination of carboplatin and paclitaxel. Although most patients experience a clinical remission after undergoing primary chemotherapy over 50% will eventually develop progressive disease. The conventional cytotoxic agents have proven to have lower response rate and higher toxicity in heavily pretreated patients [1,2]. Thus, there is a clear need for novel salvage therapeutic strategies for women with recurrent carcinoma. Over the last 3 decades, the importance of angiogenesis in tumor progression has been established. The increased vascular network results in tumor growth and expansion, which is associated with aggressive clinical behaviour and a poor prognosis. Vascular endothelial

growth factor (VEGF) is a proangiogenic molecule that stimulates vascular growth and increases vascular permeability. Because of its high expression in ovarian cancer, VEGF is a promising therapeutic target [3].

Bevacizumab, a humanized monoclonal antibody to VEGF, was approved for use in metastatic colorectal cancer by the United States Food and Drug Administration in 2004 and since then, it has been widely used in many other tumours. One phase II clinical trial proved that single agent bevacizumab was effective (21% response rate) in recurrent ovarian cancer [4]. It has also demonstrated activity when administered in combination with chemotherapy [4].

January 2008 saw publication of a phase II trial with bevacizumab-metronomic cyclophosphamide in patients with ovarian cancer who had progressed after one or two lines of chemotherapy treatment containing at least platinum and taxanes. This combination was shown to be safe and effective,

achieving a progression-free survival of 7.2 months and an overall survival of 16.9 months [5]. Metronomic chemotherapy is the frequent administration of chemotherapy at low, minimally-toxic doses with no prolonged drug-free intervals. Other phase II trials and case series have reported similar outcomes in heavily pre treated patients [6-8]. We present a retrospective analysis performed in patients treated at our institution with this combination, to investigate the efficacy and adverse effects of the monoclonal anti vascular endothelial growth factor antibody bevacizumab combined with this metronomic chemotherapeutic agent in non-protocol patients with recurrent ovarian cancer.

Material and Methods

We reviewed our institutional databases retrospectively to identify patients with recurrent ovarian, cancer who had been treated with at least one cycle of bevacizumab combination therapy. These patients were treated outside a protocol at the individual discretion of the treating physician. We provide data on the patients treated with this regimen in our hospital between 2009 and 2011. The aim of this retrospective analysis was to investigate the efficacy and adverse effects of the monoclonal anti vascular endothelial growth factor antibody bevacizumab combined with metronomic cyclophosphamide in non-protocol patients with ovarian cancer. Using our databases, we identified patients treated with bevacizumab 10 mg/kg i.v. every 2 weeks + oral cyclophosphamide 50 mg/day since January 2009 until November 2011. Patients with recurrent ovarian cancer were treated with intravenous bevacizumab 10 mg/kg every other week plus oral cyclophosphamide 50 mg daily until disease progression or undue toxicity. Responses were evaluated with Response evaluation Criteria in Solid tumors and serum CA125 Rustin criteria. Toxicity was assessed according to the Common toxicity Criteria (CTC) v.3.0. Data from 11 patients were included.

A complete response (CR) was defined as a normalization of the CA125 concentration (ie, <35 U/mL) that was maintained for at least 4 weeks. A partial response (PR) was defined as a 50% reduction in CA125 concentration that was maintained for at least 4 weeks. Progressive disease (PD) was defined as at least a 25% increase in the serum CA125 concentration for at least 4 weeks. Patients who did not meet any of these criteria were considered to have stable disease (SD). Platinum-resistant disease was defined as progression during or within six months after completing platinum therapy. Time to progression was measured from initiation of treatment until disease progression or death. The patients' performance status score was evaluated by using the Eastern Cooperative Oncology Group (ECOG) performance status scale, graded from 0 to 5. Follow-up was done through a review of medical records.

Results

Eleven patients were treated. The median patient age was 58 years; 54.5% were platinum resistant and 45.5% were platinum sensitive. The median number of previous treatments

was 4 (range 1-8). Seventy-two percent of patients had received more than 2 previous lines of treatment. A median of 21 (range 4-50) cycles of bevacizumab were administered. The overall RR was a complete response (CR) in one patient (9%), a partial response (PR) in 3 (27.3%), and stable disease (SD) \geq 6 months in 3 (27.3%). The median PFS and OS were 10 and 18 months, respectively. Thirty-nine percent of patients were progression free for at least 6 months. The grade 3-4 toxicities included anaemia [1], transient ischaemic attack [1] and hypertension [1]. Only one patient discontinued treatment as a result of toxicity, the rest continuing until disease progression. We found no cases of intestinal perforation or toxicity-related deaths; the treatment was safe and well tolerated. Patients were monitored in each cycle by way of complete blood count and basic clinical chemistry, including renal function, measurement of blood pressure and basic urinalysis.

Conclusion

In our population of heavily pre-treated patients, bevacizumab in combination with oral cyclophosphamide had significant activity without significant toxicity and with long lasting PFS.

Discussion

Prospective randomized trials have shown improvements in PFS and OS with bevacizumab plus chemotherapy in several solid tumors. To date, results from three phase II trials of bevacizumab in recurrent ovarian cancer have been presented. In the first of these, 62 patients with recurrent ovarian cancer were treated intravenously with 15 mg/kg of bevacizumab every 3 weeks. Forty-two percent of those patients had platinum-resistant disease. The overall response rate in that trial was 21% and 40.3% of patients survived progression free for at least 6 months. The investigators of a United states national Cancer institute trial reported an overall response rate to bevacizumab therapy of 24%, with 56% of patients being alive or progression free at 6 months. Then Cannistra et al. reported on 44 patients with heavily pre-treated refractory ovarian carcinoma a response rate 16% [9].

It can be said, after reviewing the literature, that combination of bevacizumab and cyclophosphamide at metronomic doses is active and well tolerated in patients with metastatic ovarian cancer, which is consistent with our results This includes the group of patients who had previously received more lines of chemotherapy, although the less-heavily pre-treated patients were found to have suffered less toxicity and achieved better results in terms of PFS and OS. In view of the results, we would conclude that it is an interesting alternative and that its use should be studied in early second-line therapy.

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