Bevacizumab in combination with metronomic oral cyclophosphamide: an effective and well-tolerated treatment for patients with recurrent ovarian cancer

C.J. Heesterbeek¹,², A.M. Thijs¹, R.H.M. Hermans³, D. Boll³, G.-J. Creemers¹

¹Department of Medical Oncology, Catharina Hospital, Eindhoven
²Department of Internal Medicine, Maastricht University Medical Centre, Maastricht
³Department of Gynaecology, Catharina Hospital, Eindhoven (the Netherlands)

Summary

Purpose of Investigation: In this study the authors describe their clinical experience with metronomic oral cyclophosphamide and bevacizumab in terms of efficacy and tolerability in patients with recurrent ovarian cancer beyond first-line treatment.

Materials and Methods: This retrospective, descriptive study included 59 patients with recurrent ovarian cancer. They were treated with intravenous bevacizumab (10 mg/kg, once every three weeks) in combination with oral cyclophosphamide (100 mg once daily). Patients had received at least one line of platinum-based chemotherapy prior to combined bevacizumab and cyclophosphamide treatment. Both platinum sensitive patients and platinum resistant patients were included. Results: Treatment with combined bevacizumab and cyclophosphamide was administered as a third line therapy in 42.4% of patients. The median number of cycles of bevacizumab administered with oral cyclophosphamide was 7 (range 1-40). A response was demonstrated in 37 (62.7%) patients, with a median progression free survival of 6 months (range 0-44). No toxicity was recorded in the medical report of 39% of patients, with only mild toxicities reported in the others. Conclusion: Bevacizumab combined with metronomic cyclophosphamide appears to be a well-tolerated and effective therapy with sustainable remissions in this selective group heavily pretreated ovarian cancer patients. This regimen should be considered in patients who are not suitable or have no need for more toxic systemic treatment.

Key words: Ovarian cancer; Bevacizumab; Cyclophosphamide; Metronomic therapy.

Introduction

Patients with ovarian cancer are diagnosed with an advanced stage of disease in about 70% of cases [1]. Over the past decades, cytoreductive surgery and first-line chemotherapy with platinum- and taxane-based chemotherapy have been demonstrated to increase disease-free survival as well as overall survival (OS) in patients with advanced ovarian cancer. Despite this improvement, most patients will suffer a relapse and eventually die due to refractory disease. Advances in chemotherapy have resulted in only marginal improvement of survival in the treatment of relapsed disease [2].

Inhibiting the activity of VEGF with bevacizumab has been shown to reduce tumour progression, ascites, and metastases in various tumour models of ovarian cancer [3, 4]. In the clinical setting, bevacizumab has been studied in the first-line treatment of patients with ovarian cancer in two large randomized phase III trials, the ICON7 study and the GOG218 study [5, 6]. Both trials reported an improvement in progression free survival (PFS), but no benefit for OS. In addition, the OCEANS and AURELIA studies investigated the addition of bevacizumab to second-line chemotherapy in platinum sensitive and platinum resistant ovarian cancer patients, respectively. Both studies also observed increased PFS, but no significant effect on OS [7-9].

In this retrospective, descriptive single centre study, the authors describe their clinical experience with metronomic oral cyclophosphamide and bevacizumab in terms of their efficacy and tolerability in patients with recurrent ovarian cancer beyond first-line treatment. Both platinum sensitive and resistant patients were included in the study.

Materials and Methods

This retrospective, descriptive study included patients with recurrent ovarian cancer treated at the Catharina Cancer Institute between January 2008 and June 2018. The study included both platinum sensitive patients (defined as recurrence ≥ 6 months after completing first line platinum based chemotherapy) and platinum resistant patients (defined as recurrence < 6 months after completing first line platinum based chemotherapy), as well as patients with refractory disease (defined as disease progression during first line platinum based chemotherapy). In patients who underwent cytoreductive surgery, the adjuvant chemotherapy after primary cytoreduction was defined as the first line of treatment. Patients had received at least one line of platinum based chemotherapy before treatment with cyclophos-
phamide combined with bevacizumab. Patients who received prior treatment with bevacizumab were excluded.

Treatment consisted of intravenous bevacizumab (10 mg/kg) once every three weeks in combination with oral cyclophosphamide (100 mg once daily). Treatment was continued until tumour progression, unacceptable toxicity, or the patient requested to stop the treatment. Patients were evaluated once every three weeks for clinically relevant toxicity and general performance.

Efficacy end points reported in this study were PFS, CA 125 response rate according to the definitions of the Gynaecological Cancer Intergroup [10], and measurable disease response if a CT scan was performed, using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [11]. The CA 125 level was measured once every three weeks. A CA 125 response was defined as a > 50% reduction in CA 125 levels compared to the pre-treatment sample and sustained during at least 28 days.

The start date for the PFS analysis was defined as the first day of the first cycle of treatment with cyclophosphamide and bevacizumab. The end date for the PFS analysis was defined as the day on which progression was identified.

Patient data were collected from medical records and were descriptively analysed using SPSS statistics software version 25. Quantitative variables were evaluated using measures of central tendency (mean and median) and scatter measures (standard deviation).

---

### Table 1. — Baseline characteristics

| Patients | N = 59 |
|----------|--------|
| **Age at primary diagnosis (years)** | 65 (38-84) |
| **FIGO stage at diagnosis** | |
| I, II | 4 |
| IIA | 1 |
| IIIB | 5 |
| IIIC | 32 |
| IV | 17 |
| **Histology** | |
| Serous | 47 |
| Mucinous | 1 |
| Endometrioid | 3 |
| Adenocarcinoma no other specified | 6 |
| Unknown | 2 |
| **Prior debulking** | |
| Yes | 49 |
| No | 10 |
| **Initial platinum response** | |
| Primary platinum sensitive | 43 |
| Primary platinum resistant | 13 |
| Primary platinum refractory | 3 |

---

**Results**

This study comprised 59 heavily pretreated patients with recurrent ovarian cancer. Patient characteristics are presented in Table 1. The median age at primary diagnosis was 65 years. Most patients were initially diagnosed with FIGO Stage IIIC (54.2%) or IV (28.8%) disease. The first-line treatment regimen in 96.6% of patients was carboplatin combined with paclitaxel. One patient received carboplatin monotherapy and another received cisplatin combined with cyclophosphamide as first line treatment.

Treatment with cyclophosphamide and bevacizumab was administered as a third line treatment in 42.4% of patients (range 2-10).

Seventy-three percent of patients were primary platinum sensitive after first line treatment, 22% were primary platinum resistant, while the remaining 5% had platinum refractory disease (Figure 1).

The median number of cycles of bevacizumab administered with oral cyclophosphamide was 7 (range 1-40). Following discontinuation of bevacizumab and cyclophosphamide treatment, 42 patients received other subsequent therapy.

A response rate of 62.7% (37 patients) was demonstrated with the bevacizumab and oral cyclophosphamide treatment. In 43 (72.9%) patients the response status was based on both the CA 125 level and CT-scan results, in 14 (23.7%) patients it was based on CA 125 only, while in 2 (3.9%) patients the response was based on CT-scan only.

The median PFS in the overall group of patients was 6 (range 0-44) months. In the subgroup of patients who responded (37 patients), the median PFS was 9 (range 2-44) months. PFS exceeded 12 months in 23% of all patients.

In the subgroup of patients who received bevacizumab plus cyclophosphamide as second or third line therapy, no difference in PFS was observed between the primary platinum resistant and sensitive patients (PFS 6.0 months vs. PFS 7.0 months, respectively). No toxicity was reported in 23 (39%) patients. Mild adverse effects (grade 1-2) reported in the remaining patients were fatigue, myalgia, gastrointestinal symptoms (nausea, diarrhoea, vomiting) and dyspnoea. Dose reduction of cyclophosphamide occurred in 20.3% of patients (12/59). Sixteen patients discontinued the treatment with cyclophosphamide because of grade 1-2 toxicity. Hypertension was reported in 7/59 (11.9%) patients and was treated with anti-hypertensive medication. No gastrointestinal perforations were reported and there were no treatment related deaths.

**Discussion**

In this retrospective study, low dose oral metronomic cyclophosphamide plus bevacizumab was administered to 59 ovarian cancer patients, the majority of whom had been heavily pretreated. The median PFS for the overall group was 6 months, whereas in the subgroup of responders a median PFS of 9 months was observed. Treatment with cy-
Cyclophosphamide and bevacizumab treatment details. *Based on platinum sensitivity after completing first line platinum based chemotherapy.

Cyclophosphamide plus bevacizumab appeared to be very tolerable, with no toxicities reported in 39% of patients and only mild toxicities observed in the others.

The study by Chura et al. [12] reported significant activity for bevacizumab plus cyclophosphamide treatment, with a response seen in 53% of a small group of 15 heavily pretreated patients. Since then a few case reports and small studies have published positive results for this combination of treatment, with response rates of 24-44% and a six-month PFS of 33-56% [13-16]. Furthermore Matulonis et al. [17] studied the addition of cyclophosphamide at the time of cancer progression in 13 patients treated with bevacizumab. They reported clinical benefit in four patients and stable disease in three patients. These results suggest possible benefits from sequential and combination chemotherapy with bevacizumab. The mechanisms responsible for the enhanced antitumour activity observed by combining VEGF-targeting agents with chemotherapy remain to be clarified. Inhibition of VEGF signalling by anti-VEGF therapy may potentiate the effects of cytotoxic drugs by inhibiting anti-apoptotic regulators or other survival mechanisms in tumour cells [18].

Currently, the role of bevacizumab in the treatment of ovarian cancer patients is still not clear. In two large phase III studies [5, 6], the addition of bevacizumab in first-line treatment resulted in marginal improvement of PFS, but not OS. In the OCEANS study [7] the addition of bevacizumab for platinum sensitive, recurrent ovarian cancer patients improved their PFS by 4 months. In the AURELIA study [8] the addition of bevacizumab to chemotherapy in platinum resistant patients prolonged their PFS by 3.3 months. Patients in the AURELIA study had not received more than two lines of chemotherapy. In the present study the subgroup of primary platinum resistant patients consisted of 13 cases. These patients received cyclophosphamide plus bevacizumab as a second, third or fourth line of treatment. No significant difference in PFS was found between primary platinum resistant and sensitive patients. The results of the OCEANS [7] and AURELIA [8] studies were incorporated into the Dutch guidelines for the treatment of ovarian cancer. These recommend adding bevacizumab to the treatment of patients with recurrent ovarian cancer. Most patients in the present study were treated before the combinations of carboplatin/gemcitabine and with addition of bevacizumab became the standard second-line treatments for platinum sensitive recurrent ovarian cancer. Hence they only received bevacizumab beyond second-line treatment.

Limitations of this study include those inherent to all retrospective studies, including immortal time bias. Because patients in the study received bevacizumab and cyclophosphamide while off a study protocol, they did not receive strict imaging to monitor disease progression. Moreover, a selected group of patients with different schedules of prior therapy were analysed. These different prior chemotherapeutic regimens make it difficult to attribute the observed PFS benefit directly to the bevacizumab plus cyclophosphamide combination.
Conclusion

In conclusion, the data from this single-centre study indicates that the regimen of bevacizumab with metronomic cyclophosphamide is well-tolerated and has sustainable remissions. It can therefore be considered for patients with recurrent ovarian cancer who have been pretreated with several lines of chemotherapy or for those who are not suitable or do not need a more toxic combination chemotherapy. Consequently, more toxic palliative chemotherapy can be postponed.

Author contributions

Heesterbeek wrote the manuscript with support from Creemers. All authors contributed to the final version of the manuscript. Heesterbeek collected the data and processed and analysed the data with supervision of Creemers. Creemers conceived the original idea.

Acknowledgments

The authors would like to thank the Catharina Hospital for providing the necessary software to perform this study.

Conflicts of interest

The authors report no conflicts of interest.

References

[1] Martin L.P., Schilder R.J.: “Management of Recurrent Ovarian carcinoma: current status and future directions”. Semin Oncol., 2009, 2, 112.
[2] Cannistra S.A.: “Cancer of the ovary”. N. Engl. J. Med., 2004, 351, 2519.
[3] Byrne A.T., Ross L., Holash J., Nakanishi M., Hu L., Hofmann J.L., Yancopoulos G.D., et al.: “Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model”. Clin. Cancer Res., 2003, 15, 5721.
[4] Gerber H.P., Ferrara N.: “Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies”. Cancer Res., 2005, 3, 671.
[5] Burger R.A., Brady M.F., Bookman M.A., Fleming G.F., Monk B.J., Huang H., et al.: “Incorporation of bevacizumab in the primary treatment of ovarian cancer”. N. Engl. J. Med., 2011, 26, 2473.
[6] Perren T.J., Swart A.M., Pfisterer J., Ledermann J.A., Pujade-Lauraine E., Kristensen G., et al.: “A phase III trial of bevacizumab in ovarian cancer”. N. Engl. J. Med., 2011, 26, 2484.
[7] Aghajanian C., Blank S.V., Goff B.A., Judson P.L., Teneriello M.G., Hussain A., et al.: “OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer”. J. Clin. Oncol., 2012, 17, 2039.
[8] Pujade-Lauraine E., Hilpert F., Weber B., Reuss A., Poveda A., Kristensen G., et al.: “Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial”. J. Clin. Oncol., 2014, 13, 1302.
[9] Aghajanian C., Goff B., Nycum L.R., Wang V.V., Hussain A., Blank S.V.: “Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer”. Gynecol Oncol., 2015, 1, 10.
[10] Rustin G.J., Vergote I., Eisenhauer E., Pujade-Lauraine E., Quinn M., Thünen T., et al.: “Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA125 agreed by the gynecological cancer intergroup (GCCG)”. Int. J. Gynecol. Cancer, 2011, 2, 419.
[11] Eisenhauer E.A., Therasse P., Schwartz L.H., Sargent D., Ford R., et al.: “New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)”. Eur. J. Cancer, 2009, 2, 228.
[12] Chura J.C., van Iseghem K., Downs L.S. Jr, Carson L.F., Judson P.L.: “Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer”. Gynecol Oncol., 2007, 2, 326.
[13] Garcia A.A., Hirte H., Fleming G., Yang D., Tsao-Wei D.D., Roman L., et al.: “Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the california, Chicago, and Princess Margaret Hospital phase II consortia”. J. Clin. Oncol., 2008, 1, 76.
[14] Jurado J.M., Sánchez A., Pajares B., Pérez E., Alonso L., Alba E.: “Combined oral cyclophosphamide and bevacizumab in heavily pretreated ovarian cancer”. J. Clin. Oncol., 2008, 2, 9, 583.
[15] Sánchez-Muñoz A., Mendiola C., Pérez-Ruiz E., Rodriguez-Sánchez C.A., Jurado J.M., Alonso-Carrión L., et al.: “Bevacizumab plus low-dose metronomic oral cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer”. Oncology, 2010, 1, 98.
[16] Barber E.L., Ziros E., Lurain J.R., Rademaker A., Schink J.C., Neubauer N.L.: “The combination of intravenous bevacizumab and metronomic oral cyclophosphamide is an effective regimen for platinum-resistant recurrent ovarian cancer”. J. Gynecol. Oncol., 2013, 3, 258.
[17] Matulonis U.A., Pereira L., Liu L., Lee H., Lee J., Whalen C., et al.: “Sequential bevacizumab and oral cyclophosphamide for recurrent ovarian cancer”. Gynecol Oncol., 2012, 1, 41.
[18] Hicklin D.J., Ellis L.M.: “Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis”. J. Clin. Oncol., 2005, 5, 1011.

Corresponding Author: C.J. HEESTERBEEK, M.D.
Department of Internal Medicine Maastricht University Medical Centre PO Box 5800 NL-6202 AZ Maastricht (The Netherlands)
e-mail: karin.heesterbeek@mumc.nl