# Long-term remission in a patient with heavily pretreated, advanced ovarian cancer achieved by bevacizumab and metronomic cyclophosphamide treatment

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**Vascular endothelial growth factor seems to be a promoter of tumor progression for epithelial ovarian cancer. New drugs such as bevacizumab, either alone or in combination with metronomic chemotherapy, suppress tumor growth and have proved to be effective in various tumor types. We present a 60-year-old patient with heavily pretreated, recurrent epithelial ovarian cancer, who received bevacizumab (10 mg/m$^2$) every 2 weeks in combination with metronomic administered low-dose cyclophosphamide (50 mg/day orally) after failing four explorative laparotomies and multiple chemotherapy regimes. At the time of writing, February 2011, she was being treated with this combination therapy for 24 months and the progression-free survival still continues. Treatment of advanced, refractory epithelial ovarian cancer with bevacizumab in combination with low-dose cyclophosphamide could be a very effective salvage treatment option in heavily pretreated patients. *Anti-Cancer Drugs* 22:1030–1033 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

In 2007, the incidence rate of ovarian cancer in the USA was 12.53 per 100 000 women and the death rate was 8.2 per 100 000 women [1]. Unfortunately, epithelial ovarian cancer (EOC) is mostly detected in advanced stages. Two-thirds of these patients develop recurrent disease and die after the failure of mostly several chemotherapeutic treatment attempts. Thus, resistance to cytostatic agents is a major challenge for gynecological oncology, and novel noncross-resistant therapeutic strategies are desperately needed. During the last decade, new therapeutic strategies have been developed, based on an advanced knowledge of the disease's molecular biology. Angiogenesis is pivotal in the course and progression of EOC and is seemingly a promising candidate for novel treatment approaches. Presently, the vascular endothelial growth factor (VEGF) is the best characterized angiogenic factor and is recognized as a major element in initiating and mediating tumor growth [2]. Bevacizumab, a humanized, recombinant monoclonal antibody against vascular endothelial growth factor has shown antineoplastic activity against several solid tumors and is therefore approved for the treatment of many entities [3–5]. The potential role of bevacizumab in the treatment of EOC is not clear yet, although aspects of the tumor biology allowed an antiangiogenic treatment to appear reasonable. Several phase II trials in an advanced disease setting partly showed impressive results [6–8]. Furthermore, metronomic chemotherapy shows antitumor effects, possibly by inhibiting angiogenesis by stimulating the release of thrombospondin [9–11]. The combination of bevacizumab and metronomically administered low-dose cyclophosphamide seems to have a specific antitumor potential, including increased antiangiogenic activity. Therefore, it represents a particularly interesting schedule [12,13].

Here, we report on the successful treatment of a 60-year-old patient with recurring, heavily pretreated EOC, using bevacizumab in combination with metronomic administration of cyclophosphamide, leading to long-term remission.

## Case

We report on a 60-year-old patient who was admitted to our institution in June 2004.

The patient was primarily diagnosed with advanced EOC, including pleural metastasis consistent with stage IV disease. She was surgically treated with total hysterectomy, bilateral salpingoophorectomy, omentectomy, and partial resection of ileum with anastomosis. However, only a suboptimal cytoreduction with residual tumor greater than 1 cm in diameter could be achieved. A pleurodesis was performed for prevention of recurrent effusions. Histopathologically, EOC with an initial tumor stage of pT3c, G3, pNx, R2, and M1 was found.

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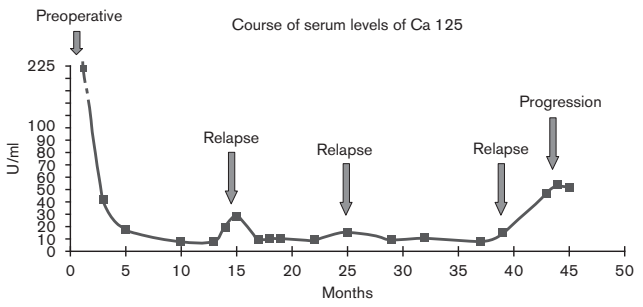
Subsequently, the patient received six cycles of combined chemotherapy consisting of carboplatin area under the curve 5 and paclitaxel (175 mg/m$^2$) d1q22, which was well tolerated. Eleven months later, cancer antigen (CA) 125 increased slowly (Fig. 1) and an MRI scan of the pelvis showed relapse of the ovarian cancer with a $10 \times 8$ cm cystic, solid tumor at the end of the vagina (Fig. 2). The patient was treated with a second explorative laparatomy with radical tumor debulking that involved a hemicolectomy with anastomosis. Debulking was again suboptimal. As part of a phase II trial, she received additional chemotherapy with six cycles of liposomal doxorubicin leading to stable disease. After another 6 months, the disease progressed again. As an individual treatment decision, a third surgical tumor debulking was undertaken followed by the reinduction of combined chemotherapy consisting of carboplatin and paclitaxel. Owing to an allergic reaction to carboplatin during the first application, this regimen had to be changed to a paclitaxel single-agent schedule (four cycles). The disease was stable for 6 months then, and progressed afterward as peritoneal carcinosis with infiltration of the pelvic side wall. Once again, as part of an individually discussed treatment concept, the patient underwent surgical tumor debulking. Palliative chemotherapy with topotecan (4 mg/m$^2$) was followed weekly. Already during cytostatic treatment with topotecan, the peritoneal carcinosis progressed again. For the first time, the patient suffered from increasing symptomatic ascites, including abdominal distension and pressure. Weekly punctures for symptom relief became necessary. An abdominal MRI scan confirmed increasing peritoneal lesions and metastasis of spleen and liver (Fig. 3a).

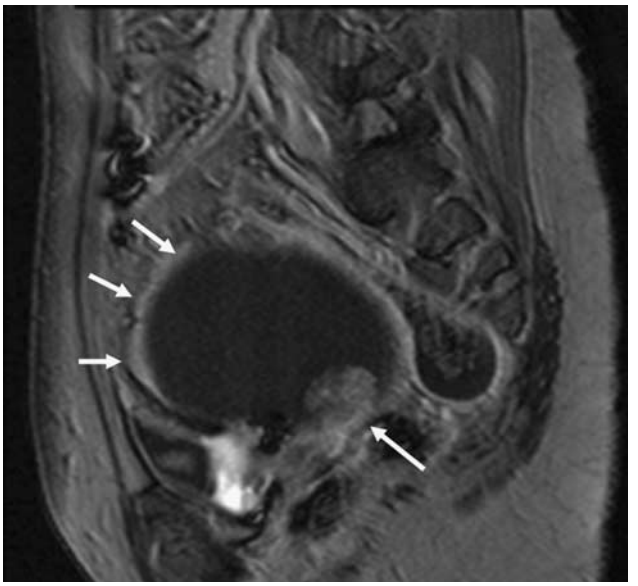
Owing to declining performance status (Eastern Cooperative Oncology Group: 2–3) and increasing symptoms, the patient was too weak for systemic intravenous chemotherapy. In the light of promising data currently published [12,13], we offered the patient an off-label salvage therapy with bevacizumab (10 mg) intravenously every 2 weeks in combination with metronomic administration of cyclophosphamide (50 mg/day orally). As

**Fig. 1**




Course of serum level of CA 125 (U/ml) before study treatment.

**Fig. 2**



MRI scan: relapse with cystic solid tumor at the end of the vagina (arrows).

supportive treatment, ranitidine (50 mg daily orally) was started concomitantly. Within 6 weeks of treatment, the patient experienced an impressive recovery from all abdominal complaints. CA 125 decreased to a normal range (Fig. 4) and no more abdominal paracenteses were necessary. Tumor response could be objectified by an abdominal MRI scan after 3 months, documenting a partial remission of both peritoneal carcinosis and hepatic and splenic secondaries (Fig. 3b).

At the time of writing, February 2011, the patient has been undergoing treatment for 24 months, with progression-free survival (PFS) still continuing. CA 125 remains within normal ranges (Fig. 4). An MRI scan of the pelvis demonstrated a radiographic complete response.

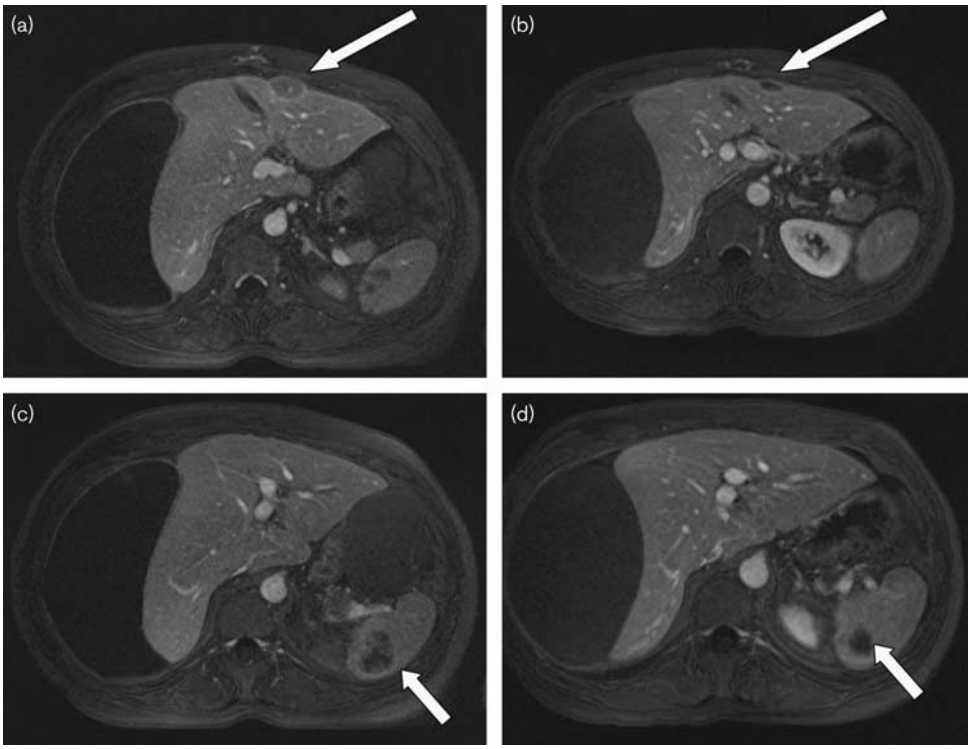
Observed toxicity included only hypertension, which was treated with an angiotensin converting enzyme inhibitor and recovered under this treatment completely.

There were no thrombotic, renal, gastrointestinal, or hemorrhagic adverse events observed. Urine dipsticks, which were performed every 2 weeks before application of bevacizumab, showed no relevant proteinuria. Currently, the patient is in fine condition and is actively taking part in her daily life.

## Discussion

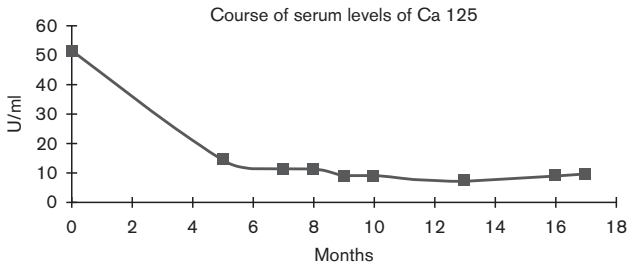
The prognosis of patients with advanced recurrent EOC after failure of multiple chemotherapy lines is commonly poor, and response rates are generally as low as 15% [14]. While aiming to define the role of alternative, noncytostatic salvage strategies, some effort has already been made to clarify the usefulness of bevacizumab. Monk

**Fig. 3**




MRI scan. (a, arrow) Increasing peritoneal lesions and (b, arrow) metastasis of spleen and liver before starting study treatment. (c and d, arrows) Tumor response due to 3 months of study treatment.

**Fig. 4**




Course of serum level of CA 125 (U/ml) during study treatment.

*et al.* [15] described 32 patients, heavily pretreated, who received a bevacizumab-based therapy. The overall response rate was up to 16% and the median PFS was 5.5 months. In a phase II study of single-agent bevacizumab ($n = 62$) by Burger *et al.* [6] response rate of 17.7% and median PFS of 4.7 months were observed. Cannistra *et al.* [7] evaluated activity of bevacizumab in a highly resistant patient population and reported a response rate of 15.9%. The 6-month PFS was 27.4%. These studies showed the significant activity of bevacizumab as a single agent in recurrent ovarian cancer. In addition to these studies, Garcia *et al.* [16] studied the usefulness of a combination of bevacizumab and metronomic low-dose cyclophosphamide in a phase II trial. On treating ($n = 70$) mostly intensively pretreated patients, the investigators observed an overall response rateof 24%. A further 55% of these patients experienced disease stabilization and the median time to progression was 7.2 months [16]. Already in 2007, Chura *et al.* [12] showed the significant activity of bevacizumab and cyclophosphamide with a response rate of 53% for a small group of heavily pretreated patients ($n = 15$). Moreover, in 2009, Sanchez-Munoz *et al.* [13] reported on two patients, also heavily pretreated because of EOC, who both showed a complete remission after the induction of bevacizumab and low-dose cyclophosphamide. After interruption of this 1-year-treatment, however, both patients experienced a disease relapse after 4 and 6 months. Despite poor prognosis, a second complete and ongoing remission was achieved by reinducing therapy with bevacizumab and cyclophosphamide. These impressive experiences are in line with the study on our treatment concept.

To our knowledge, we report on the first long-term remission in a heavily pretreated EOC patient using bevacizumab and metronomic cyclophosphamide. Taking

into account the successful reinduction of this regimen as described by Sanchez-Munoz *et al.* [13], it is observed that the combination of bevacizumab and daily low-dose cyclophosphamide not only shows the antiangiogenic and thereby antineoplastic activity but may also be a candidate for successful maintenance therapy. Results of the phase III Gynecologic Oncology Group 218 trial ($n = 1873$), currently presented at American Society of Clinical Oncology, also underscored the importance of an antiangiogenic maintenance treatment for patients with primary EOC. Women who received bevacizumab (five cycles) in combination with carboplatin area under the curve 6 and paclitaxel (175 mg/m$^2$, six cycles) followed by the continuation of bevacizumab alone for a total of up to 15 months had a median PFS of 14.1 months ($P = 0.0001$) compared with 13.1 months in women who received chemotherapy alone [17].

The major impact of this regimen on the long-term stabilization or remission of the disease may lead to a different view on the systemic treatment of EOC. Although no major complications could be found in our case and in the studies published by Sanchez-Munoz *et al.* [13], the potential side-effects of this therapy regimen, mainly gastrointestinal perforations as described by Garcia *et al.* [16], have to be considered, in particular when considering a long-term maintenance treatment. Finally, it still remains unaddressed if there are distinct molecular predictors, for example, antiangiogenesis gene polymorphisms, to select appropriate patients for successful antiangiogenic therapy. Schultheis *et al.* [18] showed the first evidence of a relationship between angiogenesis gene polymorphisms and clinical outcomes in patients with ovarian cancer treated with bevacizumab and cyclophosphamide. Their data suggest some polymorphism in the angiogenesis gene, which could be used as a molecular predictor of response to bevacizumab-based chemotherapy and progression-free survival. Further research has to determine predictive factors that are to be included in standard oncological treatments.

In summary, the combination of bevacizumab and metronomic low-dose cyclophosphamide appears to be a promising salvage option in heavily pretreated patients with advanced recurrent EOC that merits further evaluation within clinical trials, particularly, with regard to its potential value as a maintenance therapy.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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