Long-term remission of an advanced recurrent endometrial cancer in a heavily pretreated patient using a combined regimen with bevacizumab and metronomic cyclophosphamide

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The treatment of advanced endometrial cancer remains a challenge and the range of valuable treatments remains limited. Recently, the monoclonal vascular endothelial growth factor–antibody bevacizumab as a single-agent regimen or in combination with different chemotherapeutic approaches has been approved as a therapeutic option for several solid tumors. First, clinical trials evaluating the use of bevacizumab in endometrial cancers have been completed, but the results have not been published yet. A 59-year-old patient with advanced recurrent endometrial cancer presented at our institution suffering from increasing abdominal discomfort. She had been extensively pretreated using radiotherapeutic approaches and multiple chemotherapeutic regimens. The level of cancer antigen 125 (CA 125) was rising and a cystic pelvic mass was detected, consistent with a persistent local tumor relapse. As several cytotoxic treatment attempts had failed, we decided to induce a combined therapy with bevacizumab (intravenously) and metronomic cyclophosphamide (orally) as an individual treatment option. After 6 weeks of treatment, the patient's abdominal complaints had completely disappeared, CA 125 had decreased significantly to nearly baseline levels, and the previously detected cystic pelvic mass could no longer be seen. No significant side effects could be observed besides a mild fatigue. During the following weeks, CA 125 levels continued to decrease, and the patient experienced a long-time remission in fine condition for 10 months before PD. Bevacizumab in combination with metronomic cyclophophamide can be a well-tolerated salvage treatment option for patients with advanced, heavily pretreated recurrent endometrial cancer that exacts further evaluation within clinical trials. *Anti-Cancer Drugs* 22:822–824 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Approximately 13% of all patients with primary endometrial cancer develop recurrent disease [1]. In the treatment of recurrent endometrial carcinoma, different therapeutical modalities consisting of radiotherapy, surgery, and systemic approaches such as hormone therapy or chemotherapy are in use, but the options are limited and alternative salvage therapies are needed [2]. Most of the patients are treated with chemotherapy in a palliative setting. Medical trials of chemotherapeutic combinations include combinations of doxorubicin and cisplatin, cyclophosphamide or paclitaxel and carboplatin [2].

Recently, several phase III trials evaluated the use of the vascular endothelial growth factor–antibody bevacizumab in metastatic solid tumors such as breast and colorectal cancers showing promising improvement in the overall survival and progression-free survival [3].

In the search for new systemic therapeutic options in endometrial cancer, therapies for epithelial ovarian cancer (EOC) are of particular interest. As EOC and adenocarcinomas of the endometrium are both of Müllerian duct origin, they have some histological similarities and the efficacy of several treatment attempts is often similar as well [3]. Phase II trials in ovarian cancer showed the activity of bevacizumab in combination with other modalities such as low-dose metronomic cyclophophamide. In addition, this therapy is normally well tolerated even by heavily pretreated patients with a weak performance status [3].

There is only little information available so far on the efficacy of bevacizumab for the treatment of patients with endometrial cancer. At present, only one clinical trial is being conducted by the Gynecologic Oncology Group, with data presented at the 2009 American Society of Clinical Oncology annual meeting showing overall response rates (ORRs) of 15% [4].

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Case report

We report the case of a 59-year-old woman who was referred to our institution in September 2009 with advanced recurrent endometrial cancer.

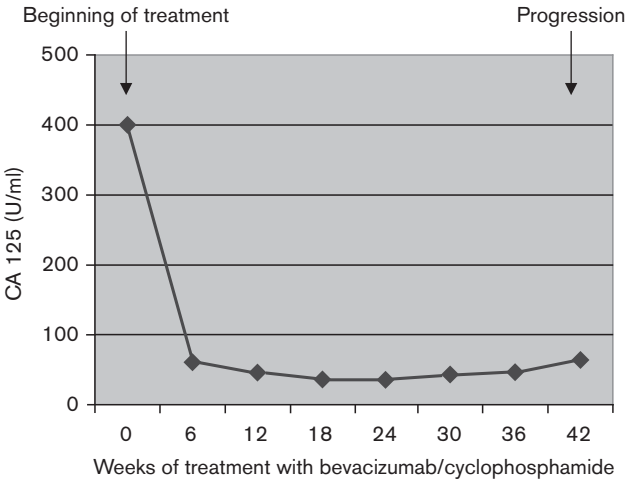
In 2004, the patient was primarily diagnosed with endometrial cancer and underwent a total abdominal hysterectomy and bilateral salpingoopherectomy. Histopathologically, an endometrioid endometrial cancer was found with an initial tumor stage of pT1b pNX M0 R0 G2. No further adjuvant treatment followed primary therapy. In 1993, a colorectal cancer stage of pT2 pN0 M0 G2 had been treated by extended hemicolectomy with normal follow-up examinations.

In 2007, the patient relapsed showing multiple peritoneal tumor manifestations with infiltration of the pelvic sidewall. Owing to the intraperitoneal dissemination of the disease, there was no possibility for radical debulking surgery and the patient received a palliative external beam radiation of the pelvic field. Despite ongoing radiation, the tumor showed further progression, so that radiotherapy was interrupted after application of a cumulative dose of 11 Gy and a palliative chemotherapy consisting of carboplatin (area under the curve) 5 and paclitaxel (175 mg/m^2) d1q22 was started. During chemotherapy, all symptoms were rapidly relieved and after six cycles of the treatment, a complete remission could be found. After 9 months, the peritoneal carcinosis progressed again and several palliative chemotherapeutic regimens including carboplatin/paclitaxel agent, pegylated liposomal doxorubicin and topotecan were administered. The reinduction of paclitaxel/carboplatin led to a progression-free survival of 12 months, whereas the tumor progressed rapidly after a few weeks of treatment with pegylated liposomal doxorubicin and topotecan.

In September 2009, the patient presented with increasing abdominal discomfort while undergoing chemotherapy with topotecan. A gynecologic examination showed no relevant findings. Transvaginal sonography showed a cystic pelvic mass of 6×11 cm in diameter, which was quite consistent with the previously reported findings in that patient. In contrast, the level of CA 125 had risen from 273 to 401 U/ml under the current treatment.

Led by the strong clinical impression of a tumor progression confirmed by the increasing course of CA 125, we induced a salvage therapy with bevacizumab (10 mg/kg) administered intravenously and 50 mg of cyclophosphamide administered orally per day. After 6 weeks of treatment, the patient recovered from all abdominal complaints, the level of CA 125 fell to 59.2 U/ml, and the cystic pelvic mass disappeared in sonography. Besides a mild fatigue consistent with a grade 1 toxicity according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), the patient had no relevant adverse effects. The patient experienced a long-time remission in fine condition for 10 months before PD. After ten months CA 125 increased significantly and abdominal sonography revealed ascites (Fig. 1).

Fig. 1



Course of cancer antigen 125 (CA 125).

Discussion

There is no standard treatment for patients with recurrent endometrial cancer after failure of several treatment approaches. As many of these patients are still in good clinical condition and are willing to receive further therapeutic attempts, there is a need for alternative salvage options. Platinum-based chemotherapy regimen is the mainstay of most first-line treatments, but in contrast, the preferred antineoplastic drug in a second-line or third-line setting is not clarified [2].

Ovarian cancer and endometrial cancer have some histological features in common, and are therefore often susceptible to the same therapeutic approaches.

Monk *et al.* [5] published their experiences with bevacizumab-based treatment regimen in 32 patients with advanced recurrent EOC after failure of multiple cytototoxic treatment lines, reporting impressing ORRs of up to 16% and stable disease rates of up to 62.5%. In particular, a treatment with bevacizumab in combination with orally administered low-dose cyclophosphamide is of interest as a metronomic application of cyclophosphamide is assumed to enhance the antiangiogenic efficacy of bevacizumab. In 2008, Garcia *et al.* [6] published a phase II trial evaluating this combined regimen on 70 patients, confirming a remarkable ORR of 24%.

The experiences with bevacizumab for the treatment of endometrial cancer are limited. Kamat *et al.* [7] showed in a series of 111 patients with endometrial cancer that half of the patients had increased levels of vascular endothelial growth factor, associated with a poor outcome. In an orthotopic mouse model of endometrial cancer, the

combination of docetaxel and bevacizumab was more efficacious than the application of a single agent.

Wright *et al.* [8] carried out a retrospective analysis of 11 women patients with recurrent uterine neoplasms treated with bevacizumab in combination with a cytotoxic agent. Two of the patients showed a partial remission, which was achieved using a combination with oral cyclophophamide.

To our knowledge, we show for the first time that treatment with bevacizumab and oral metronomic cyclophophamide can be an exceptionally well-tolerated and excellent therapeutic option in advanced recurrent and heavily pretreated endometrial carcinoma.

Future trials must be carried out to prospectively improve the efficacy of bevacizumab and metronomic cyclophophamide in patients affected by advanced endometrial cancer.

Acknowledgements

Conflicts of interest

None declared.

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