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Case Series

Metronomic cyclophosphamide with bevacizumab provides disease stabilization in patients with advanced uterine cancer

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humanized version of this antibody, significantly improves outcome in various human tumors when combined with cytotoxic chemotherapy. In a phase II study, the combination of metronomic cyclophosphamide with bevacizumab has shown promising activity in recurrent ovarian cancer (Garcia et al., 2008). Although, metronomic chemotherapeutic regimens have been used in a variety of solid tumors, the data on patients with endometrial cancer is limited. Here, we present two patients with advanced uterine cancer that were treated with the combination of metronomic cyclophosphamide and bevacizumab. Pathology type for the first and second was endometrioid and uterine papillary serous (UPSC), respectively. With this regimen the patients achieved prolonged disease stabilization and improved quality of life.

Introduction

Targeting angiogenesis in order to achieve tumor control was introduced by Folkman in 1971 (Folkman, 1971). Inhibition of angiogenesis can be achieved with the use of targeted therapies that affect critical steps in tumor vascularization or with the administration of cytotoxic agents in a metronomic regimen. Conventional chemotherapy is typically administered in 3–4 week cycles at the maximal tolerated dose. Metronomic chemotherapy is achieved by frequently administering doses that are significantly lower than the maximal tolerated dose. In the time interval between consecutive cycles the host can recover from adverse effects and the vascular damage can be rapidly repaired. Although the cancer cells have less chance of recovering, regrowth of part of the tumor can occur, especially if the drug-free period is too long. It has been shown that shortening the drug-free period increases the anti-angiogenic effects of cytotoxic drugs. An additional advantage in continuous low-dose chemotherapy is the minimization of toxic side-effects, while allowing combination with selective inhibitors of angiogenesis (Mross and Steinbild, 2012).

Vascular endothelial growth factor (VEGF) is recognized as a major element in regulating angiogenesis. In animal models, VEGF plays a major role in mediating tumor growth while the VEGF monoclonal antibody has an inhibitory effect. Bevacizumab, the recombinant

Case 1

A 56 year-old nulliparous black female initially presented with complaints of irregular vaginal bleeding for the past 4 years and a 30 lb weight loss over the course of 3 months. Physical exam showed an obese woman with fullness of the right adnexa, 16-week uterus, midline, enlarged cervix and gross tumor exiting the os. Family history was unremarkable. An endometrial biopsy was obtained and revealed moderately differentiated endometrial carcinoma of the endometrioid type. CT abdomen and pelvis showed a left adnexal cystic/soft tissue mass (9 × 9.6 cm), a left lower quadrant cystic mass (4.6 × 7.2 cm) with a mural nodule and multiple hypodense hepatic lesions, the largest measuring 2.2 × 2.5 cm, suggestive of metastatic disease. Tumor markers were as follows: CA-125 1553 U/ml, CA 19-9 1491 U/ml and CEA <0 .5 mcg/L. Given the multiple liver metastases, a primary optimal cytoreduction was not considered feasible and the patient was offered neoadjuvant chemotherapy with 3 cycles of carboplatin/paclitaxel and plan for interval debulking. Imaging after the completion of the chemotherapy course showed no interval change.

In addition, the patient had worsening bleeding requiring a blood transfusion and the decision was made to proceed with surgical management. The patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oopherectomy (BSO), resection of peritoneal metastatic implant and a liver biopsy. The findings were as follows: 15 week uterus, 20 × 20 cm solid left adnexal mass, along with a 5 × 8 cm peritoneal implant adjacent to the left paracolic gutter and multiple lesions on the surface of the liver consistent with metastases. The patient was suboptimally debulked with residual disease at the liver. Final pathology was FIGO Grade II

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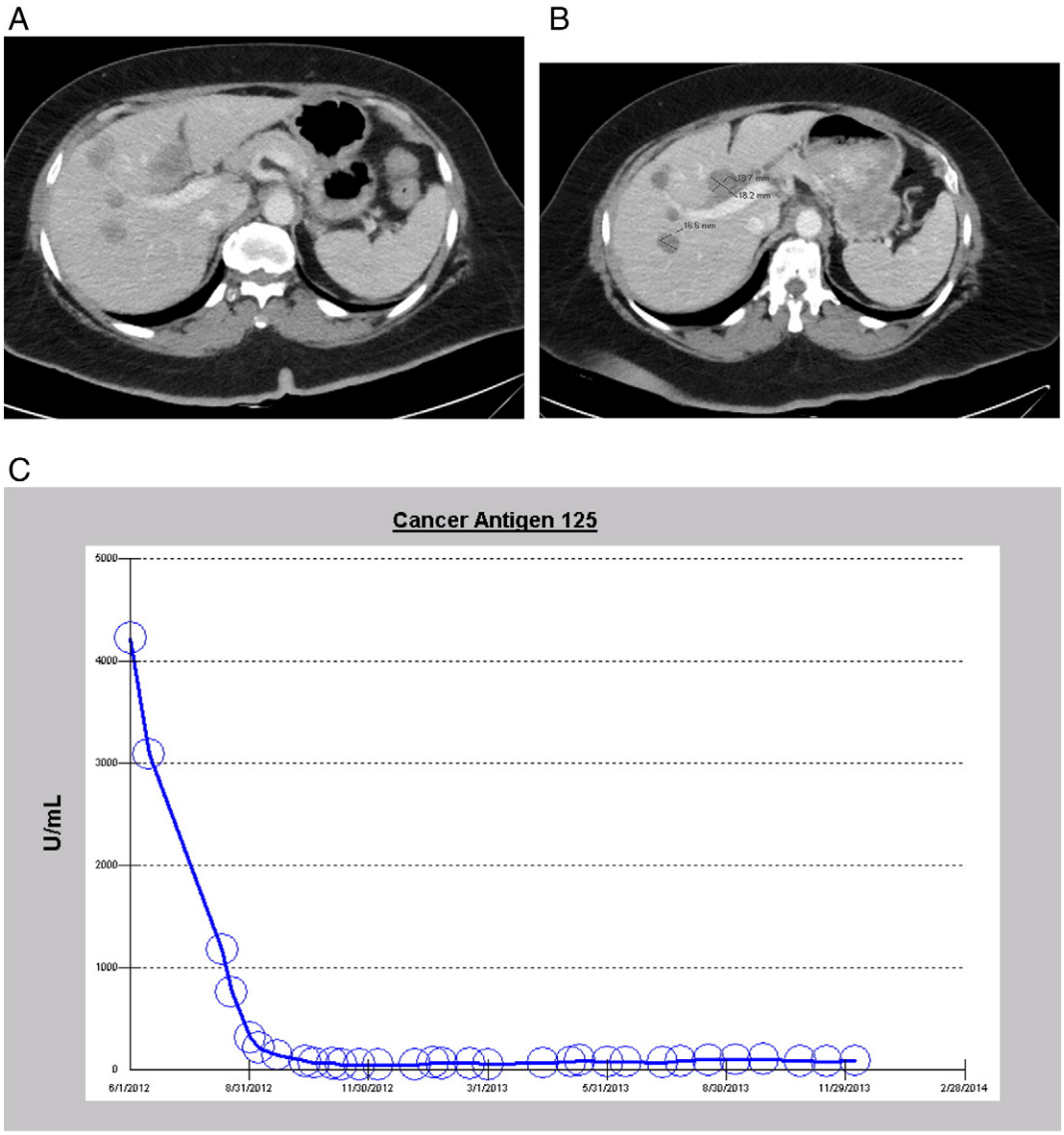

Fig. 1. A. CT Abdomen shows multiple metastatic lesions (left). Stable metastatic liver lesions after 12 months of treatment with metronomic cyclophosphamide and bevacizumab (right). B. Disease stabilization with metronomic cyclophosphamide and bevacizumab in patient with advanced endometrioid adenocarcinoma as evidenced by CA-125 levels.

endometrioid adenocarcinoma with depth of invasion 2.8 out of 3 cm and lymphovascular space invasion. Tumor size was 7.5 cm with involvement of both the anterior and posterior aspect of the endometrial cavity, cervical stroma, bilateral tubes and ovaries, left paracolic gutter and the liver. The patient was assigned a FIGO (2009) stage IVB endometrioid adenocarcinoma. Chemosensitivity studies (Precision Therapeutics) demonstrated resistance to all cytotoxic chemotherapeutics. The patient was started on a metronomic regimen consisting of cyclophosphamide 50 mg daily and bevacizumab 15 mg/kg every 3 weeks. This regimen was in place for 16 months while disease stabilization was achieved as evidenced by interval imaging (Fig. 1A). The sum of longest dimensions of target lesions was 65 mm on baseline CT before the initiation of the metronomic regimen, 55 mm after 6 months of treatment and 61 mm after one year of treatment. Serial measurements of CA-125 are consistent with biochemical response to therapy (Fig. 1B). During this time, the patient reported a good quality of life. The metronomic therapy was interrupted due to a Stage IV non-healing decubitus ulcer. Of note, the patient has been wheelchair bound for 10 years secondary to a spine injury. Subsequently, her disease progressed rapidly and she expired 2 months later.

Case 2

A 73 year-old black female Para 3 initially presented with complaints of abdominal pain, increased abdominal girth, nausea and vomiting for one week. Physical exam showed an obese woman with a distended abdomen that was tender to palpation. Bowel sounds were hyperactive. Pelvic exam revealed a 20-week size pelvic mass. Family history was unremarkable. CT abdomen and pelvis showed small bowel obstruction with transition point in the distal jejunum. There was a heterogeneous mass measuring 7.3 × 6.5 cm extending from the uterus to the left adnexa and causing small bowel obstruction. There was paraaortic, retroperitoneal and mesenteric lymphadenopathy. Multiple hypodensities consistent with metastases were seen in both lobes of the liver, the largest measuring 2 × 4 cm. CA-125 level was 135 U/ml. Given the clinical picture of small bowel obstruction, the patient was taken to the operating room and underwent an exploratory laparotomy, radical hysterectomy, BSO, tumor debulking, small bowel resection in 3 segments and anastomosis, partial cystectomy, cystotomy repair and ureteral stent placement, omentectomy, appendectomy, pelvic lymphadenectomy. The operative findings were as follows: 10 × 20 × 20 cm mass involving

the uterus, bilateral tubes and ovaries, small bowel, sigmoid colon and appendix. Two tumor nodules measuring 2 cm each in the omentum.

Innumerable subcentimeter tumor nodules in the surface of the liver. Three cm tumor plaque on the dome of the bladder. Gross adenopathy in left pelvic sidewall. At the completion of surgery, there was gross residual disease in the liver.

Histology was consistent with UPSC involving the small bowel, omentum, appendix and bladder. Right tube and ovary, cervix, parametria and lymph nodes were positive. Final pathology was Stage IVB uterine papillary serous carcinoma. The treatment plan was adjuvant chemotherapy with carboplatin and paclitaxel. One week after the administration of the first cycle the patient presented to the emergency room with neutropenic urosepsis. She was treated with parenteral antibiotics (cefepime) and G-CSF (filgrastim). After she recovered, she declined any further cytotoxic chemotherapy. At that time, the option of metronomic chemotherapy with cyclophosphamide and bevacizumab was discussed and the patient agreed to pursue the latter treatment option. With the metronomic regimen, her disease remained stable for 16 months as evidenced by CA-125 monitoring (Fig. 2) and CT imaging. During that period of time the patient was asymptomatic. Eventually, her disease progressed in the pelvis causing bilateral obstructive nephropathy and the patient expired shortly thereafter. Total survival time status-post surgery was 18 months.

Discussion

The combination chemotherapy with carboplatin and paclitaxel has emerged as the treatment of choice for patients with advanced uterine cancer (Miller et al., 2012). For patients with poor response to the standard first line treatment, the options are limited and there is no standard of care regarding salvage treatment. Therapy typically employs either second line cytotoxic chemotherapy or hormonal agents. Based on data from GOG studies, cytotoxic chemotherapy for advanced or recurrent disease provides a median progression free survival of 8 months and the goal of care is usually palliation (Fleming et al., 2004). Moreover, the conventional chemotherapeutic regimens use the maximum tolerated doses and are often associated with severe, sometimes life threatening, side-effects.

Therefore, the introduction of new strategies with at least equivalent efficacy and decreased toxicity is highly desirable. Metronomic chemotherapy is designed to maintain stable disease for advanced cancer patients with minimal toxicity. It has been suggested that frequent administering of low-dose chemotherapy targets the dividing endometrial cells and inhibits the formation of tumor-associated capillaries. This hypothesis is supported by in vitro data showing selective cytotoxicity of low-dose chemotherapy for human vascular endothelial cells. Other mechanisms which have been proposed include the induction of endogenous inhibitors of angiogenesis, the activation of apoptotic pathways and the inhibition of recruitment of progenitor endothelial cells. The daily low-dose cyclophosphamide has demonstrated remarkable efficacy and tolerability in various animal models. Metronomic regimens have been associated with favorable responses in patients with various advanced solid tumors. A phase II study showed that the combination of metronomic cyclophosphamide with bevacizumab can be effective and well tolerated in patients with recurrent ovarian cancer. The response rate in this study is favorably compared to other conventional or investigational treatment modalities for recurrent ovarian cancer (Garcia et al., 2008).

The use of metronomic regimens in the treatment of advanced uterine cancer is supported by in vitro data showing that angiogenesis plays an important role in the growth of uterine tumors. Furthermore, a higher expression of VEGF has been documented in malignant compared to benign or hyperplastic endometrium (Abulafia et al., 1995). Limited clinical data on the use of the combination of metronomic chemotherapy with bevacizumab in patients with advanced uterine cancer who failed multiple conventional chemotherapies suggest the potential for therapeutic benefit (Wright et al., 2007). In our cases, the progression free interval exceeds the previously reported median progression free survival for patients treated with conventional or investigational regimens.

Additionally, the patients continued to report a good quality of life during their progression-free survival interval. None of the common side effects of Bevacizumab such as hypertension and bowel perforation occurred in our cases. Bevacizumab might have contributed to the non healing decubitus ulcer in Case 1. Metronomic therapy is commonly regarded as the 'last resort' for patients with advanced malignancies

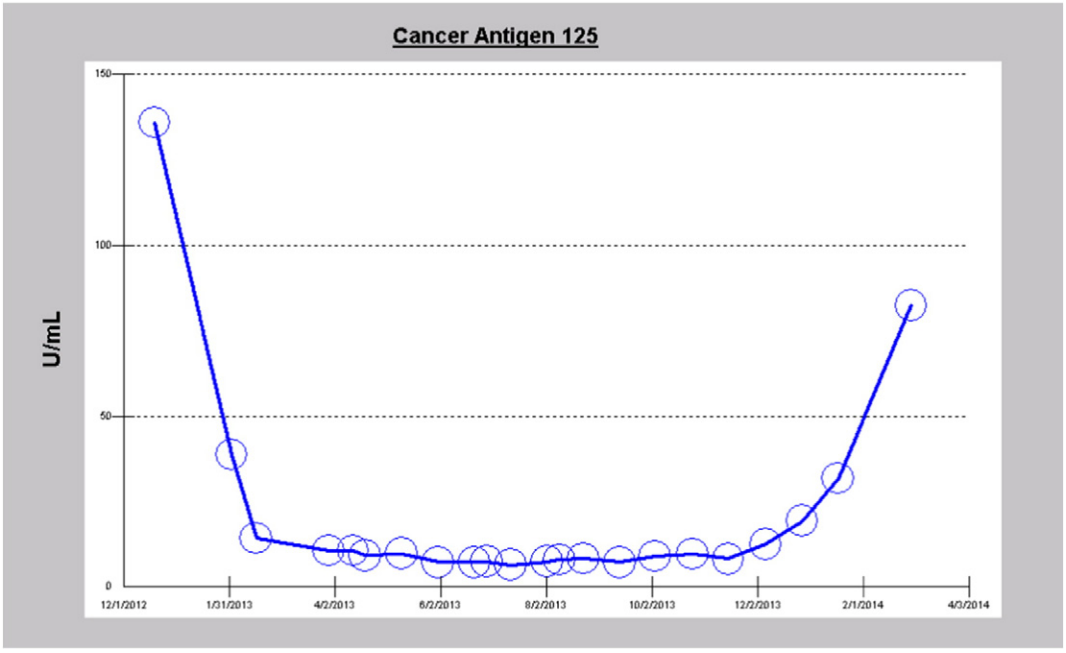

Fig. 2. Disease stabilization with metronomic cyclophosphamide and bevacizumab in a patient with UPSC as evidenced by CA-125 levels.

when multiple cytotoxic regimens have failed and before withdrawal of anti-cancer treatment. One of the recognized benefits of anti-angiogenic therapies is control of ascites formation in patients with carcinomatosis through the inhibition of malignant vascularization and stabilization of tumor capillaries (Anon., 1995). In our case the tumors were purely solid and they were stabilized with the anti-angiogenic therapy. Frequently, concerns about the toxicity related to bevacizumab and cost considerations lead providers to attempt a number of cytotoxic agents before a metromonic regimen. This delay may have a negative impact on the main objectives of metronomic treatment, which are disease stabilization and maintenance of quality of life. The implementation of the metronomic regimen relatively early in the course of the disease while the patient is still in good performance status and before the tumor load becomes overwhelming, may be associated with a higher response rate.

Furthermore, starting the metronomic therapy early may reduce the risk for life threatening toxicities of bevacizumab that are associated with a higher tumor load like thromboembolism and bowel perforation. The concept of early implementation of metronomic therapy is more applicable in tumors with inherent resistance to cytotoxic chemotherapy, like the endometrioid- type endometrial cancer.

In conclusion, the presented cases suggest that the combination of metronomic cyclophosphamide with bevacizumab can be an effective strategy against tumor progression in patients with advanced uterine cancer when first line chemotherapy fails. Controlled randomized trials comparing conventional versus metronomic regimens are required in order to define optimal drug combinations with maximal anti-tumor activity and minimal toxicity.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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