

Long Term Combination Treatment With Bevacizumab, Pegylated Liposomal Doxorubicin and Regional Abdominal Hyperthermia in Platinum Refractory Ovarian Cancer: A Case Report and Review of the Literature

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Abstract. *Background: Platinum resistance constitutes a therapeutic challenge in the treatment of ovarian cancer, with overall unsatisfactory response rates to standard chemotherapy and correspondingly low survival. Regional abdominal hyperthermia and bevacizumab are treatment options that have both shown the capacity to improve the results of standard chemotherapy in the platinum-resistant situation, when added to the treatment schedule. Case Report: We report on a 29-year-old patient with primary platinum-refractory ovarian cancer, who was treated with a combination of pegylated liposomal doxorubicin, regional abdominal hyperthermia and bevacizumab in a four-week cycle over a long-term period of 38 months. Due to an excellent clinical and radiologic response resulting in stable disease, with a concomitant mild toxicity profile consisting only of intermitted diarrhoea and mild fatigue, the treatment was continued in an ambulatory setting. Discussion: To our knowledge we describe the first experience with combination treatment of pegylated liposomal doxorubicin with regional abdominal hyperthermia and bevacizumab in a long term setting of almost 2 years. Excellent response with comparably low toxicity was demonstrated. Further evaluation as a therapeutic option in this heavily pretreated and highly palliative patient population is warranted.*

The subgroup of patients with platinum-resistant or -refractory ovarian cancer constitutes a special collective with an overall unfavourable prognosis (1, 2). In the platinum-resistant group, response rates to standard chemotherapy, such as monotherapy with pegylated liposomal doxorubicin or topotecan are generally expected at approximately 17-20%, while in the platinum-refractory group, response rates are even lower at 5-10% (2). Great efforts have been made to improve treatment options for this unfavourable patient subpopulation. While combination regimes did not demonstrate any significant survival benefits over monotherapies, various other options are currently under investigation based on the concept of targeted treatment strategies (1). One of the most promising agents is bevacizumab, which targets neoangiogenesis through direct blockage of the vascular endothelial growth factor (VEGF) pathway (3). This agent demonstrated satisfying results both in the first-line as well as in the recurrent setting and provided response rates comparable to standard chemotherapy in the platinum-resistant condition when used as a mono therapy (4).

Regional abdominal hyperthermia (RHT) constitutes an additional promising therapeutic option in ovarian cancer relapse and has found increasing application in daily clinical management. Recent data demonstrated promising activity in combination with topotecan or PLD in various pre-clinical and early phase I trials (5, 6). The mode of action implicates an additional stress for the tumor cells by exposure to high temperatures, denaturation of tumor-related proteins and apoptosis induction, as well as an increase in susceptibility to concurrent chemotherapy (7, 8).

While both bevacizumab and RHT are well suited for combination therapy with standard chemotherapy due to their limited range of side-effects, a combination regime of chemotherapy with RHT and bevacizumab has not yet been described for patients with ovarian cancer to the best of our

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Key Words: Hyperthermia, bevacizumab, doxorubicin, platinum-refractory, ovarian cancer.

knowledge, especially applied over a long period of almost 2 years. In the present report, we describe the first experience to the best of our knowledge of such an innovative approach in a young patient with primary platinum resistant ovarian cancer and multiple systemic and operative pre-treatments.

Case Report

We report on a 29-year-old patient with ovarian cancer. The patient was first diagnosed with stage IIIc disease in September 2005 and underwent median incision laparotomy with radical surgery consisting of bilateral salpingo-oophorectomy and hysterectomy, omentectomy, pelvic and para aortal lymphonodectomy, pelvic deperitonealization and sigmoid resection with primary anastomosis. A macroscopic tumour-free situation was achieved during surgery. First-line adjuvant chemotherapy was conducted with 6 cycles of systemic carboplatinum and paclitaxel between November 2005 and March 2006. Only two weeks after the sixth cycle of primary chemotherapy, abdominal and transvaginal sonography were suspicious for relapse and recurrent disease was confirmed in April 2006, when the patient underwent a re-laparotomy that revealed peritoneal carcinomatosis. Second-line chemotherapy was started with treosulfan and gemcitabine over four cycles until July 2006 when progressive disease was diagnosed. Another laparotomy with suboptimal tumor debulking (tumour residuals >2 cm) and creation of a colostomic stoma due to bowel involvement was subsequently performed in September 2006. The patient was then referred to our centre, where a staging CT scan revealed a singular liver lesion and pelvic and mesenteric lymph node metastases. Chemotherapy with IV PLD 40 mg/m² (d1) was started in November 2006 and combined with RHT (d1) in a four-week cycle. RHT was applied using a SIGMA 60 applicator. The patient received a total of 27 RHT treatments. The therapy was performed with an average of 1740 W, a total treatment time of about 85 min, of which heating time consisted of about 25 min and steady state temperature over 60 min. The average intraabdominal temperature was 41.7°C (min 40.7°C, max 43.8°C) with an average vaginal / bladder temperature of 2° C lower (40.3°C). (5) Bevacizumab at 7.5 mg/kg was added to the treatment schedule in January 2007. A follow-up CT scan revealed a partial response in May 2007. The treatment was continued in a four week-cycle and subsequent CT scans and clinical examination resulted in the diagnosis of stable disease untill March 2010, when the gynaecological examination was finally suspicious for progressive disease, revealing recurrence of the tumour to the pelvis. Treatment was then interrupted and the patient underwent re-laparotomy for tumour debulking after discussion of the treatment options and because of maximal treatment wish of the patient. During the tumor debulking operation in March 2010, a partial resection of the ileum and subtotal colectomy with ileorectal anastomosis was performed. A macroscopically tumour-free

situation was achieved. There were no noticeable intraoperative findings apart from mild adhesions. The patient recovered uneventfully after the operation with good healing of the anastomosis and was discharged 10 days after surgery. The tumour board recommended adjuvant chemotherapy with gemcitabine and bevacizumab, but the patient died of unknown cause two months after the operation. Pulmonary embolism was hypothesized as a possible cause of death; an autopsy was refused.

Up to that point the patient had received a total of 32 cycles of PLD over a period of 38 months and 29 cycles of bevacizumab over a period of 37 months and had remained in a stable condition. The treatment was continued beyond the usual period in this long term fashion after informing the patient of the possible risks and side-effects and because of the maximal treatment desire of the patient as well as the beneficial side-effect profile. Treatment with bevacizumab was paused multiple times during this period for different reasons, such as patient request and postoperative pause after stoma closure. As side-effects of the treatment the patient described mild intermittent diarrhoea and mild fatigue (grade I CTC) as the only symptoms. Arterial hypertension or wound healing complications were not observed at any time during treatment with bevacizumab.

Discussion

The addition of RHT to a chemotherapy and anti-angiogenetic combination therapy for recurrent ovarian cancer is very unusual but not without a rationale. Regional abdominal hyperthermia obtains a direct cytotoxic effect through apoptosis induction, but also has the capacity to enhance the therapeutic effectivity of chemotherapeutic and immunologic agents alike (5). This effect is mediated through impairment of cellular repair mechanisms and enhanced intracellular uptake, as well as a variety of temperature-dependent physiological factors, such as perfusion, tumour microenvironment and vessel penetration (7, 8). The combination of RHT with bevacizumab in particular might have a strong synergistic effect that overwhelms the merely additive effects of RHT and bevacizumab alone, and might be explained as follows: In contrary to physiological blood vessels which can exist without high levels of VEGF, tumour-related micro vessels are dependent on a continuous supply with this factor in order to maintain their stability. This explains why termination of VEGF with bevacizumab was shown to lead not only to inhibition of neoangiogenesis, but also to the destruction of tumour-related blood vessels. In this situation of already very suboptimal perfusion due to bevacizumab-mediated destruction of micro vessels, maximum apoptosis-inducing effect might be achieved when tumour tissue is forced into an increased need for oxygen by means of hyperthermia.

The novel combination of PLD, RHT and bevacizumab given over a long-term period, as reported for this case, was effective in our patient with platinum-refractory ovarian cancer. Even though this regimen and its continuation beyond a period of six cycles in the fashion of a maintenance therapy is far from any guideline recommendation, the result of stable disease over 38 months is remarkable. This result might be based on the independent as well as mutual enhancement of cytotoxic effects of the three treatment modalities. Bevacizumab, as one of the most potent anti-angiogenetic agents, was shown to be an effective monotherapy in platinum-resistant ovarian cancer. The first results for bevacizumab in combination to standard chemotherapy in platinum-resistant ovarian cancer are very promising and the agent is currently under further evaluation in this setting with the AURELIA trial.

Another major aspect of this report is the good side-effect profile observed in this case. The patient did not report any toxicities apart from intermittent diarrhea and mild fatigue. Even though a single experience with this novel regimen does not warrant any speculations about the safety profile, the side-effects of PLD, RHT and bevacizumab did not show any negative interaction or cumulative toxicity of the different components. Nevertheless, long-term effects of this combination could include hypertension, wound-healing complications and fistula caused by bevacizumab and cardiac toxicity as the main concern in the long-term use of PLD, even though recent studies demonstrated a good cardiac safety profile for this agent in the long-term use (9). Despite the fact that this first experience is promising, the efficacy and safety profile of this combination must be evaluated in a prospective trial in order to legitimise its future use in patients with platinum-resistant and -refractory ovarian cancer.

Conclusion

The combination of PLD, hyperthermia and bevacizumab resulted in the outcome of partial response and subsequent stable disease over a total period of 38 months in this case of platinum-refractory ovarian cancer. This first experience might suggest that this new combination is active in platinum-refractory and platinum-resistant ovarian cancer and evaluation in a future prospective trial could be warranted.

Acknowledgements

We thank our technical assistant Ms Solveig Jentsch (Department of Radiotherapy, Charité University Medicine of Berlin) for her enthusiasm in treating patients with RHT.

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Received March 16, 2011

Revised July 5, 2011

Accepted July 6, 2011