Case 2 – Trabectedin as a new opportunity in the multidisciplinary approach to the advanced ovarian cancer: report of a long-term survival case

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Abstract
We present a particular and explicative case of long-term survival bilateral ovarian cancer, heavily pre-treated, in which disease stabilization was achieve with the use of pegylated liposomal doxorubicin and trabectedin. This case is also of interest in that it investigates the benefit of cytoreductive and palliative surgery for bowel obstruction in the second or subsequent relapse in epithelial ovarian cancer. Our experience shows that the multidisciplinary treatment modality in these complex cases – combining both medical and surgical modalities – also involving new agents, such as trabectedin, should ensure a consistent and equitable approach to planning and managing care for advanced ovarian cancer in order to offer each of our patients the best strategy for improving survival and quality of life.

Key words: advanced ovarian cancer, trabectedin

Introduction

Trabectedin is a marine-derived antineoplastic agent. It is indicated in Europe in combination with pegylated liposomal doxorubicin for the treatment of platinum-sensitive, recurrent ovarian cancer; it is also approved for use in patients with advanced soft-tissue sarcoma who have progressed despite receiving previous treatment with anthracyclines and ifosfamide or in those who are unsuited to receive these agents [1]. When combined with pegylated liposomal doxorubicin (PLD), trabectedin improves progression free survival (PFS), overall survival (OS) and overall response rate (ORR) over PLD alone with acceptable tolerance in recurrent platinum-sensitive ovarian cancer patients [2].

We present a particular and explicative case of a long term survival bilateral ovarian cancer, heavily pre-treated, that obtained disease stabilization from the use of PLD and trabectedin. This case shows also interest for investigate the benefit of cytoreductive and palliative surgery because of bowel obstruction in the second or subsequent relapse in epithelial ovarian cancer.

Case presentation

On March 2002, a 47-year-old-woman without previous pathological history underwent bilateral salpingo-oophorectomy and omentectomy for bilateral ovarian serous papillary adenocarcinoma with lymph node and omentum metastasis. After surgery she started adiuvant chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC5); 1 cycle was only administered for suspected reaction to paclitaxel, including pruritus and erythema (rapid resolution with the suspension of therapy and the use of steroid). She continued with carboplatin (AUC5). After 6 cycles, she underwent second-look surgery: the histological examination was negative. She continued with clinical and instrumental follow-up. One June 2005, due to a rapid increase in CA125 serum level (to 145 U/mL), a choline positron emission tomography (PET) scan was performed, which showed evidence of multiple abdominal metastasis. The patient was treated with a first-line treatment with docetaxel (75 mg/m^2) and carboplatin (AUC5) for 8 cycles, after which the choline PET was negative and the CA125 level had returned to baseline; subsequently, on June 2006, she underwent third-look surgery with negative histological examination.

On September 2006, a CT scan revealed a peritoneal relapse of disease. A second line of chemotherapy with PLD (40 mg/m^2) was performed with partial remission (PR) at imaging evaluation. On December 2007, after 10 cycles, for progression of disease (PD), she started a third line of chemotherapy with carboplatin (AUC5) and gemcitabine

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(1200 mg/m^2) for 6 cycles: subsequent CT scan revealed peritoneal PD. Chemotherapy with weekly topotecan (3.75 mg/m^2) was started (fourth line). On March 2009, a fourth-look surgery was performed with a removal of the relapse, transverse colon, jejunum, small pancreas, splenectomy and lymphadenectomy. The pathology report was metastasis from ovarian serous papillary adenocarcinoma. On May 2009, a re-challenge with docetaxel (75 mg/m^2) and carboplatin (AUC5) as fifth line was chosen; after 6 cycles a CT scan revealed peritoneal PD, in a general situation of likely resistance to chemotherapy. No results were obtained with subsequent letrozole (oestrogen receptor = 15%, progesterone receptor = 0%). On March 2010, she started sixth chemotherapy line with PLD (30 mg/m^2) and trabectedin (1.1 mg/m^2) administered by 24-hour infusion every 21 days. The chemotherapy was continued for 5 cycles. Stable disease (SD) was seen at the follow-up CT scan (Figure 1) and clinical benefit was seen in terms of reduction of subocclusive status, permitting removal of the nasogastric tube. Considering both the SD, the clinical benefit and the psychological distress of patient regarding any type of oncological treatment we decided to stop chemotherapy.

On January 2011, after a few months without therapy, the patient' occlusive status worsened and she underwent an end-to-end anastomosis and ileostomy. Eastern Cooperative Oncology Group (ECOG) performance status was 2. After collegial discussion, considering the strongly pretreated disease, we decided to use weekly paclitaxel with pharmacological prophylaxis for allergic reactions, without any improvement both in term of PFS and clinical benefit (the treatment was stopped after 4 cycles). We assisted to a progressive worsening of ECOG performance status and we continued with palliative care; in May 2011, unfortunately the patient died of disease progression.

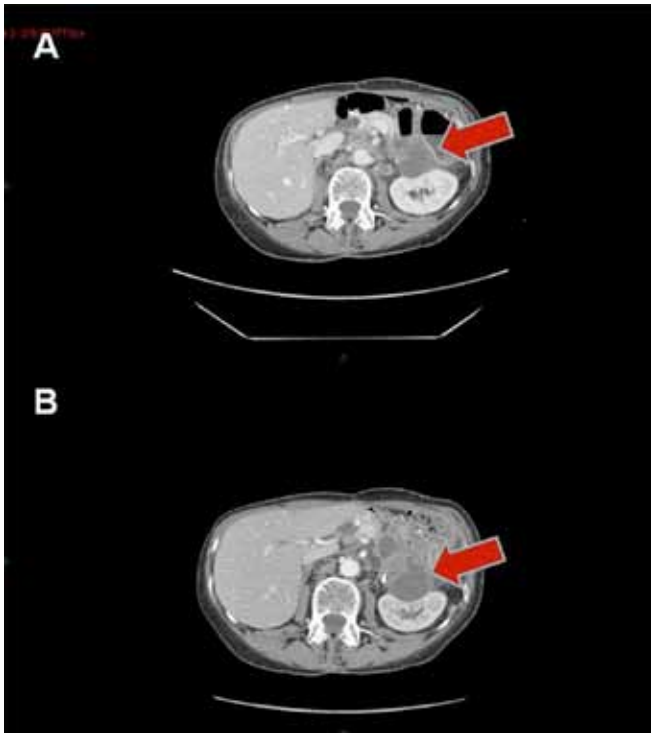

Fig. 1. CT scan shows an abdominal mass, near to the left kidney, with increasing intra-lesional contrast enhancement for low-density colliquative aspects before (A) and after (B) trabectedin treatment.

Discussion

The recent improvement in survival in ovarian cancer is probably due to progress in treatment: regimens combining taxanes (paclitaxel and docetaxel) with platinum compounds are now generally recommended as first-line treatment for women with advanced disease. Different agents are available for second-line and subsequent therapy following progression on platinum and taxanes in advanced ovarian cancer patients with platinum-sensitive disease. Trabectedin is a new, active, multitarget and well-tolerated treatment for patients with epithelial ovarian cancer who experience disease relapse after platinum and taxanes; the reported results on tolerability, clinical efficacy, and durability demonstrate the potential usefulness of trabectedin in providing an alternative to existing single agents [3-6] or combination treatments for ovarian cancer [1, 2]. Our experience represents an explicative case of long-term survival with advanced ovarian cancer (more than 9 years) that was treated with all possible available agents alone or in combination. In this case, we obtained disease stabilization in a heavily pre-treated patient, confirming an increasing role of trabectedin in the management of advanced ovarian cancer, prolonging survival in patients receiving subsequent-line platinum. The toxicity profile of the combination of trabectedin with PLD has shown also to be predictable and manageable, with no association with cumulative end-organ toxicities (renal, cardiac, or neurological toxicities) and different toxicity profile from other second-line strategies without the presence of inconvenient side effects, such as alopecia, hypersensitivity reactions, hand-foot syndrome, or mucositis [7]; in the present case we had no adverse events, and the treatment was well tolerated, except for the presence of asthenia (grade 2). The other peculiarity is the importance of surgery in the management of our disease, with several consecutive laparotomies (four surgeries in total in our case). There were substantial differences in the spectrum and complexity of procedures performed in patients with advanced ovarian cancer with tendency towards more complex surgery (selected bowel and upper abdominal procedures are also performed). Negative second-look

laparotomy does not preclude recurrence and subsequent look-laparotomies could be necessary for management of this complex disease. The literature (more frequently retrospective data) indicate that complete resection of recurrent tumour formations should be the aim, since survival prolongation is mainly seen in patients with no residual disease in order to offer the best therapeutic chances to patients and to protect patients with limited life expectancy from additional surgical burden [8]. Moreover, advanced ovarian cancer patients who have undergone multiple surgeries and multiple chemotherapy regimes, often present with acute or subacute intestinal obstruction as a preterminal debilitating event. Usually these are multilevel obstruction where surgical effort may not be possible or may not be useful. In a select few patients, the entire proximal bowel up to the mid or distal ileum may be unobstructed with a multilevel obstruction below this point. Such a patient may benefit from an ileostomy. This may have been the situation with this case. Our experience shows that the multidisciplinary treatment modality in these complex cases, combining both medical and surgical modalities, also involving new agents, such as trabectedin, should ensure a consistent and equitable approach to planning and managing care for advanced ovarian cancer in order to offer each of our patients the best strategy for improving survival and quality of life.

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Commentary

Dear Readers,

I decided to be the first to write in this 'Meet the expert' section in order to establish a methodology. Second opinions, debates, multidisciplinary approaches are an important part of our everyday professional life. We will analyze in this section simple clinical cases in order to focus on, criticize and discuss practical questions.

Dr Giuliani et al. present a woman with 13 years of clinical history of ovarian cancer and seven lines of chemotherapy. They highlight that trabectedin was moderately effective, with a stabilization lasting 5 months, when given as sixth-line treatment, but I believe the most important point of discussion and my first question is: is it possible to chronicise the disease, and is this the right patient to achieve this goal? The possibility of making ovarian cancer a chronic disease is not applicable to all patients, but this case is probably the right one. Receiving more lines of effective platinum-based chemotherapy suggests BRCAness in this patient. BRCAness means that patients have a higher possibility of responding to chemotherapy even when they are resistant to platinum-based regimens. Liposomal doxorubicin, trabectedin and, of course, platinum, being the drugs that interact with DNA, have more chance of activity in these patients due to the defective DNA repair. This is not the case for taxanes. This hypothesis seems verified in the patient reported here. However, studies are ongoing with trabectedin in both BRCA-mutated and BRCAness patients to verify this hypothesis.

The second point regards the multidisciplinary approach with several surgical interventions performed in this case. Surgery is fundamental in ovarian cancer. This is clear for primary cytoreduction, where the possibility to achieve a residual tumour = 0 is the best prognostic factor in

ovarian cancer, and is under evaluation in phase III studies in patients at the time of platinum-sensitive recurrence.
This patient underwent second-look surgery twice after platinum-based chemotherapy. Second-look is a procedure that should not be performed anymore, since there are data demonstrating that it does not improve the outcome of the disease. Is it useful to have an early diagnosis of progressing or recurrent disease by using second-look procedure or a PET scan? I believe that data clearly indicate that anticipation of the recurrence on therapy does not prolong survival. In asymptomatic patients, early therapy may worsen quality of life – one of the most important endpoints in the recurrence setting. Thus, second-look surgery and PET scans are not part of my usual clinical strategy. I still use PET only the recurrence setting when this sensitive examination may help in the surgical decision in selecting the cases suitable for surgery.

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