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Case report

Individualized long-term chemotherapy for recurrent ovarian cancer after failing high-dose treatment

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Chemotherapy for recurrent ovarian carcinoma (ROC) produces response rates of 10–80% depending on the prevalence of platinum resistance. Most patients relapse within 1 year and median progression-free survival is generally no more than 6 months. Newly developed ATP chemosensitivity assays (ATP-TCA) offer the opportunity for individualized therapy and have shown promising results compared to standard regimens. We report on an unusual case of long-term survival in a patient with stage III c ovarian cancer failing postoperative platinum-based high-dose treatment who subsequently underwent repeated chemotherapy over a period of 4 years. The chemotherapy protocol was selected by pretherapeutic *ex vivo* ATP-based chemosensitivity testing of autologous tumor tissue. To our knowledge, this is one of the few cases of ROC in which partial remissions using conventionally dosed chemotherapy were achieved repeatedly despite a unfavorable relapse-free interval after high-dose chemotherapy for primary disease. We conclude that ATP-TCA-directed chemotherapy for ROC can select active and tolerable regimens even in difficult therapeutic situations in which no standards recommendation exists. [© 2002 Lippincott Williams & Wilkins.]

Key words: ATP tumor chemosensitivity assay, long-term chemotherapy, recurrent ovarian cancer.

Introduction

In western countries, ovarian cancer has the highest mortality among gynecologic malignancies. Current standard therapy consists of maximum cytoreduction with subsequent platinum- and paclitaxel-based chemotherapy.[1] Despite increasingly successful primary therapy, clinical chemoresistance develops in the majority of patients, resulting in a 5-year survival rate of only 25%.[2]

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Patients presenting with recurrent tumor must be considered incurable. Palliative procedures may, however, extend life expectancy or increase symptom-free periods. The likelihood of patients responding to salvage chemotherapy depends on the relapse-free interval after completing first-line chemotherapy. Patients relapsing after 12 month or more have a good chance to respond to re-induction with platinum, whereas patients relapsing within 6 months or less have a particularly poor chance to respond to any salvage chemotherapy. High-dose chemotherapy for primary ovarian cancer, which may improve cure rates in selected cases, has recently been under clinical phase III evaluation. Little information exists how to treat patients presenting with recurrent disease after this intensive treatment modality. Due to its palliative nature, post-primary chemotherapy for ovarian cancer should be of low toxicity and high convenience for the patient. Furthermore, despite the limited life expectancy of patients with recurrent ovarian carcinoma (ROC), the quality of life should not be unduly diminished.

Case report

A 44-year-old Caucasian patient, gravida 0, menarche at 13, increased hereditary risk of neoplasm due to a BRCA mutation. An increase of serum lactate dehydrogenase was first discovered during a routine internal examination in July 1996. A subsequent coloscopy revealed an impression of the sigma. A computed tomography scan of the abdomen revealed ascites, a peritoneal carcinomatosis and a suspicious right ovary. In September 1996 a radical operation was performed with bilateral salpingoophorectomy, hysterectomy, omentectomy, splene-

octomy, pelvic and para-aortic lymphonodectomy, and resection of the colon transversum. Histological examinations showed a moderately differentiated, infiltrating endometrioid adenocarcinoma of the ovary, FIGO stage IIIc. At the end of operation, residual tumor of 2 cm or less was left i.p. The patient then entered a recent German phase II trial of postoperative high-dose chemotherapy in advanced ovarian cancer. On both 10 November 1996 and 4 December 1996 the patient was given two induction cycles of cyclophosphamide (5.7 g/m^2) and paclitaxel (330 mg/m^2) in order to mobilize peripheral blood progenitors which were harvested by leukopheresis 14 days after each chemotherapy course.

High-dose chemotherapy followed on 22 December 1996 and 18 January 1997 with carboplatin (2250 mg/m^2) and paclitaxel (450 mg/m^2) with subsequent stem cell transplantation. The third high-dose cycle which was administered on 16 February 1997 consisted of etoposide (200 mg/m^2), carboplatin (2200 mg/24 h) and melphalan (140 mg/m^2).

In January 1998 the patient was transferred to our department with an increased CA-125 level (59 U/l). A gynecological examination lead us to moderately suspect a recurrent tumor of the vaginal cuff subsequently confirmed histologically by biopsy. Consecutively, the tumor was tested *ex vivo* for chemosensitivity using the ATP-based tumor chemosensitivity assay (ATP-TCA). The results of the chemosensitivity assay are shown in Figure 1. This assay utilizes a commercially available kit technique (TCA 100; DCS Innovative Diagnostik Systeme, Hamburg, Germany). Detailed ATP-TCA methodology has been described elsewhere.[3]

The tumor proved to be optimally sensitive to cisplatin combined with gemcitabine, which was chosen for second-line chemotherapy with cisplatin

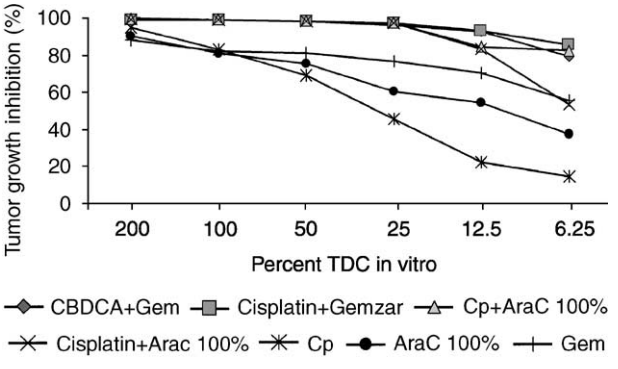

Figure 1. Results of an *ex vivo* chemosensitivity assay examining the recurrent tumor after failing high-dose treatment.

at 75 mg/m^2 and gemcitabine at 1250 mg/m^2. We recommended a minimum of six cycles at 21-day intervals. At the patient's request therapy was terminated after three cycles. During therapy, the tumor marker CA-125 decreased below 30 U/1.

The patient presented with a newly relapsing tumor in November 1999. Intestinal obstruction had developed as a result of rapidly growing peritoneal carcinomatosis with malignant ascites. CA-125 was 72 U/l. The *ex vivo* chemosensitivity of the tumor, which was again tested by ATP-TCA, showed moderate sensitivity to gemcitabine while still being optimally sensitive to gemcitabine in combination with cisplatin. Due to considerable acute toxicity related to preceding chemotherapies, the patient refused another platinum-based treatment. Therefore, four cycles of this drug were given as monotherapy with 1000 mg/m^2 day 1 and 15 every 4 weeks. During this therapy the tumor marker remained unchanged and the patient experienced long-lasting disease stabilization. The good performance of the patient was not adversely influenced by this treatment.

Progression of disease occurred in February 2000. The patient presented with diffuse intrahepatic tumor spread and subileus due to a progressive peritoneal carcinomatosis. Therefore, ileostomy was performed in the surgical department of the University of Cologne Medical School. After recovery from surgery, the patient requested another palliative chemotherapy. Regarding the high activity seen with gemcitabine plus cisplatin in prior ATP-TCAs performed, re-induction was considered a logical next therapeutic step. Due to the patient's refusal to undergo further platinum, we decided to substitute platinum by treosulfan according to an actual phase II protocol being active in our institution.[4] Therapy consisted of treosulfan (5000 mg/m^2) day 1 and gemcitabine (1250 mg/m^2) day 1 and 8, q3w. Five cycles of this regime were administered until June 2000. The tumor marker CA-125 again became negative during therapy and the patient was free from progression for almost 6 month.

Subsequently the patient was re-induced with treosulfan and gemcitabine. With this treatment both the patient's condition and the tumor marker remained constant for 4 months.

In February 2001 lymph node enlargement in the right axilla and a suspicious focus in the right breast were detected at routine check-up. A biopsy was performed and lymph node histology showed a metastasis of a poorly differentiated adenocarcinoma. This was considered a metastasis of the ovarian cancer.

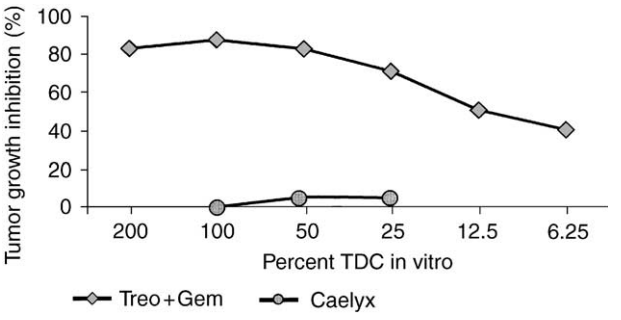

Figure 2. Results of an *ex vivo* chemosensitivity assay examining malignant ascites after fifth-line chemotherapy.

The general performance of the patient at this time was good. At her own request, the highly motivated patient was given fifth-line chemotherapy with liposomal doxorubicin (Caelyx®; 20 mg/m). However, during the first therapy cycle a massive increase of the liver metastases occurred. Chemotherapy was interrupted after the first cycle. Subsequently the patient developed malignant ascites which interestingly evidenced the tumor to be at least partially sensitive to treosulfan and gemcitabine while exhibiting complete resistance to high dose-doxorubicin (Figure 2). Due to the dramatic deterioration of the patients performance we obstained from further administrating systemic therapy.

Discussion

In ovarian cancer no clear guidelines exist in regard to second-line treatment of the disease. More than 50% of women diagnosed with ovarian cancer can be expected to develop recurrent disease and require multiple secondary treatment regimens. No clear standards exist with respect to the optimal duration of chemotherapy. In the past, the value of maintenance therapy has been the subject of controversy and strongly questioned. Different studies examining the benefit of a long-term chemotherapy were performed in advanced and metastatic breast cancer.[5] The authors of these examinations could show a benefit in regard to progression-free survival with continuous chemotherapy in contrast to intermitant short-term therapy. However, the overall survival was the same in both groups. In ovarian cancer the matter has not been well studied. In Europe, for example, less than 10% of patients with ROC are included in randomized studies. Patients with advanced ovarian cancer who experience tumor recurrence following primary chemotherapy can be divided into two therapeutic groups: 'platinum sensitive' and 'platinum resistant'. The interval between previous chemotherapy and subsequent recurrence is one of the most important prognostic factors for response to subsequent therapy.[6] Patients with a platinum-resistant tumor have a poor prognosis. There is a wide range of treatment options, including standard treatments and experimental therapies, but the response rate of most anticancer drugs is below 20%. Some of the agents demonstrating activity in patients with recurrent platinum-resistant advanced ovarian carcinoma include: taxanes, gemcitabine,[7] oral etoposide,[8] topotecan[9] and vinorelbine. Since the response rates achieved with these drugs are similar, patient convenience, side effects and cost may play a significant role in drug selection. However, little information exists at present on how to treat patients presenting with recurrent disease failing high-dose platinum-based chemotherapy after a relatively short period of time. Pretherapeutic chemosensitivity testing using the ATP-TCA has provided promising results in both breast and ovarian carcinomas.[10] The assay has been successfully used to select active drugs and combinations in situations where no empirical standard exists. Individualized chemotherapy offers the opportunity to avoid ineffective treatments with unnecessary side effects. The patient presented here, who may be considered unlikely to respond to anything from a conventional point of view, experienced repeated responses or at least disease stabilization to salvage therapy guided by individual chemosensitivity testing without suffering from adverse effects significantly affecting the quality of life. Thus our report may be considered another good example how the ATP-TCA can select active and tolerable regimens even in difficult-to-manage therapeutic situations in which no standard recommendation exists.

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