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Case report

Effective treatment of a patient with a high-grade endometrial stromal sarcoma with an accelerated regimen of carboplatin and paclitaxel

Piotr W Szlosarek,[1] Fiona J Lofts,[1] Ruth Pettengell,[1] Paul Carter,[2] Martin Young[3] and Clive Harmer[4]

Departments of [1]Medical Oncology, [2]Gynecologic Oncology and [3]Histopathology, St George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, UK, [4]Department of Radiotherapy, The Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK.

The rarity of endometrial stromal sarcoma (ESS) and its poor response to treatment provides fertile ground for investigational therapies. An accelerated regimen of carboplatin and paclitaxel is investigated. A patient with a recent history of treated tuberculosis of the lung represented with infertility and acute abdominal pain from suspected fibroids, and underwent a laparotomy with a diagnosis of a high-grade ESS. A novel therapeutic approach using a regimen of carboplatin and paclitaxel with the reinfusion of filgrastim-mobilized peripheral blood progenitor cells is described. A partial response was observed following six cycles of chemotherapy. Grade IV thrombocytopenia occurred after the last cycle, with recovery prior to pelvic radiotherapy. The patient remained well 1 year post-diagnosis. High-grade ESS is responsive to combination chemotherapy with paclitaxel and carboplatin, and requires further evaluation. The use of an accelerated regimen may also have contributed to the response and this question awaits randomized trials. [© 2000 Lippincott Williams & Wilkins.]

Key words: Carboplatin, endometrial stromal sarcoma, filgrastim, paclitaxel, peripheral blood progenitor cells.

Introduction

High-grade endometrial stromal sarcoma (ESS) is a rare tumor of the uterine tract with a poor prognosis, due to both its grade and predisposition for early hematogenous spread. Although a number of case series have been reported, there is no overall consensus as to a standard chemotherapy regimen following cytoreductive surgery. The patient described in the following case report achieved a good partial response using an accelerated regimen of carboplatin and paclitaxel. This case also illustrates the difficulties experienced when evaluating infertility on a background of recent tuberculosis.

Case report

A 36-year-old Asian housewife, gravida 0, para 0, resident in the UK for the last 4 years, presented with an 18 month history of infertility, and a 9 month history of dysmenorrhoea, pelvic pain and occasional dyspareunia. Two years previously, she had been treated for pulmonary tuberculosis (TB) and abdomino-pelvic ultrasonography at that time revealed a right subserous fibroid as well as a right tubo-ovarian mass. The latter disappeared on rescanning and abdominal TB was suspected although never proven. A year prior to the current presentation she had been referred by her general practitioner for investigation of infertility, but in view of her recent TB this was not pursued further.

Clinical examination revealed a pelvic mass consistent in size with an 18 week pregnant uterus with bilateral adnexal fullness. Ultrasonography confirmed a large, consistent with fibroids uterus arising from the pelvis and extending up to the level of the umbilicus. In view of deteriorating abdominal pain over the area of the suspected fundal fibroid, a myomectomy was planned.

Correspondence to P Szlosarek, Department of Medical Oncology, St George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, UK.
Tel: (+44) 20 8725-5815; Fax: (+44) 20 8725-0158;
E-mail: speter@sghms.ac.uk

However, she was admitted acutely 1 month later with severe lower central abdominal pain radiating to the back. A diagnosis of fibroid degeneration was made and she proceeded to a laparotomy. This revealed para-aortic lymphadenopathy, a gangrenous appendix and three large friable uterine masses (a 25 cm diameter fundal mass, a 6 cm diameter posterior mass and a 6 cm diameter anterior mass) with adherent omentum. A partial debulking procedure was performed with omentectomy and appendectomy but with preservation of the uterus, as it was considered that in the context of metastatic disease an attempt at total hysterectomy would have been hazardous and would not have contributed to the overall prognosis. The final histology confirmed a high-grade ESS, with extensive necrosis and a high mitotic index of 14 mitoses per 10 high-power fields (see Figure 1). The diagnosis was made both from conventional hematoxylin & eosin stains with confirmation from immunocytochemical investigations. The conventional appearances showed a tumor which was undifferentiated and without any features of epithelial differentiation. A full panel of immunocytochemical stains was performed and all the epithelial markers (Cam 5.2, EMA and BerEP4) were negative. Staining for vimentin was focally positive. Other markers for neural and smooth muscle differentiation were also negative. These findings all support the diagnosis of a high-grade ESS. Both the omentum and appendix were infiltrated by tumor. Staging was completed with computerized tomography (CT, see Figure 2) and tumor markers (CA125, CEA and CA199 were all negative). Her renal function was assessed with [^{51}Cr]EDTA clearance.

Informed consent was obtained and she proceeded to receive an accelerated regimen of carboplatin and paclitaxel, which involved administering carboplatin (AUC 6) and paclitaxel (175 mg/m^2) every 2 weeks, with daily filgrastim or recombinant human granulocyte colony stimulating factor (rhG-CSF), to both support and mobilize blood progenitor cells (BPCs). Isoniazid was prescribed for TB prophylaxis. The BPCs were harvested by venesection of 2 U of whole blood on day 1, with reinfusion 24 h later; the chemotherapy was given immediately following the venesection. BPC release and yield in the venesected product was monitored by CD34 flow cytometric analysis and hempoietic colony assays grown in soft agar. Clinically, the palpable mass in the lower abdomen arising from the pelvis disappeared after the first treatment cycle. After six cycles a partial remission of the pelvic mass was documented (see Figure 3). Toxicity was limited to grade IV thrombocytopenia which recovered prior to consolidation of the partial remission with radiotherapy. This was administered in two phases: 45 Gy in 25 fractions to the pelvis and para-aortic nodes, and 10 Gy in five fractions to the pelvis over 6 weeks. The patient remained well 6 months after completion of radiotherapy, but subsequently relapsed with intra-abdominal disease and died 16 months following the original diagnosis.

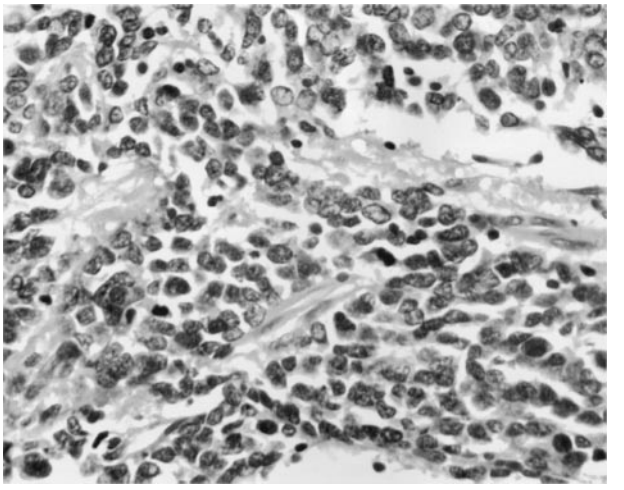

Figure 1. High-power view of tumor showing cells all resembling the stromal cells of proliferative endometrium. Note enlarged vesicular nuclei, with prominent chromatin and nucleoli, and indistinct cell borders.

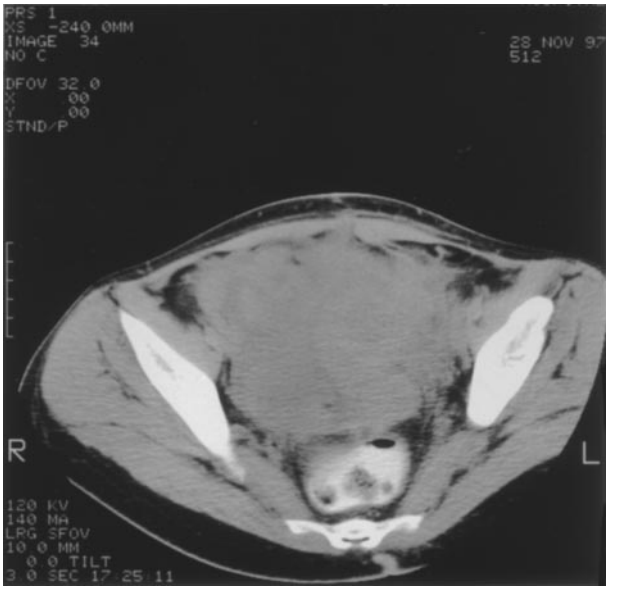

Figure 2. Pre-chemotherapy pelvic CT scan on 28 November 1997: a large residual pelvic mass with compression of the bladder.

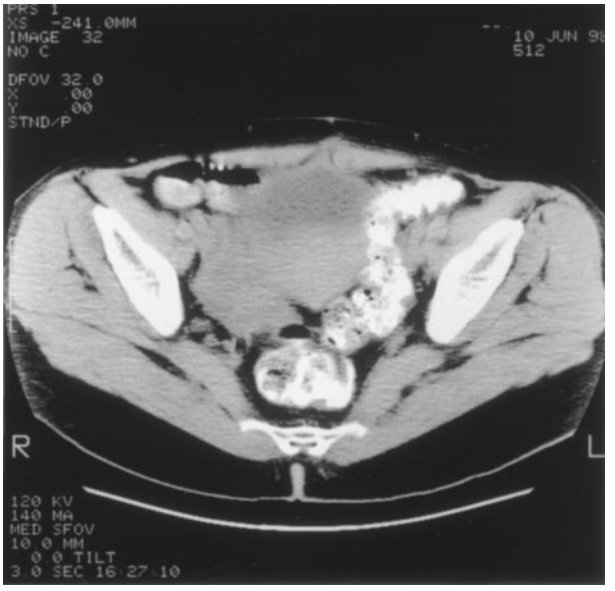

Figure 3. Post-chemotherapy pelvic CT scan on 10 June 1998: a partial remission of the pelvic mass with the bladder no longer significantly compressed.

Discussion

High-grade endometrial stromal sarcoma represents less than 5% of uterine sarcomas, which constitute approximately 3% of all uterine malignancies.[1] Prognostic factors include the mitotic index, which is expressed as the number of mitoses per 10 high-power fields (HPF) in active areas (i.e. >10 mitoses/10 HPF), the degree of nuclear anaplasia and the extent of disease at diagnosis. The mortality quoted in a number of case reviews approaches 100%, with a median survival of 312 days in a study by De Fusco *et al.*[2] Two other reviews record survival ranges of 0.1–2.3[3] and 0.1–6.2 years.[4]

The rarity and poor prognosis of ESS has hampered attempts at standardization of therapy. A recent Sarcoma Meta-Analysis Collaboration,[5] examining the adjuvant setting, emphasizes the importance of dissecting out treatment responses according to tumor sub-type.[6] In the context of ESS, the importance of subclassification into low-grade (previously uterine endolymphatic stromal myosis) and high-grade tumors is now well recognized. The former is treated with surgery and hormonal manipulation (occasionally, with systemic chemotherapy for metastatic disease), whereas the latter is treated with a combination of surgery, chemotherapy and radiotherapy.[7–9]

The most active and least toxic chemotherapy regimen for high-grade ESS, however, remains to be defined. The largest series, a collection of 21 patients treated with ifosfamide chemotherapy, showed an overall response rate of 33.3%, with three patients achieving a complete response and four obtaining a partial response.[10] This was accompanied by seven patients with grade 3 or more toxicity (granulocytopenia, anemia, neurotoxicity and renal impairment) and median response duration of 3.7 months (duration 1.4–14.9 months). In the setting of leiomyosarcoma, the addition of doxorubicin to ifosfamide doubles the response rate, although a similar series has not been reported for ESS.[11] The role of doxorubicin has been assessed either alone or in combination in 10 patients with recurrent ESS, with a 50% response rate,[12] and a randomized study comparing doxorubicin with and without dacarbazine (DTIC) quotes an 18–20% response rate with about 50% of the tumors being ESS.[13] In addition, there is evidence in sarcomas that dose intensification of anthracyclines has advantages over conventional administration.[5] The remainder of the literature contains a number of mostly single-case reports of drug activity including cyclophosphamide, vincristine, doxorubicin and DTIC combinations.[7,14]

More recently, the role of platinum agents has been explored, in combination with doxorubicin, with reports of activity.[15,16] Carboplatin, in view of its superior non-hematological toxicity profile, is preferred by some centers to cisplatin in the treatment of gynecologic tumors, with reports of similar efficacy in ovarian carcinoma.[17] A phase II study of carboplatin in patients with soft-tissue sarcomas, receiving doxorubicin as their only prior systemic treatment, demonstrated useful activity with three complete and three partial responses, and a response rate of 16%.[18] In addition, carboplatin has produced responses both as a single agent and in combination, in sarcomas of the uterus.[19,20]

The appearance of the taxanes has not escaped the attention of those in the soft-tissue sarcoma field. A phase II study of paclitaxel using a dose of 250 mg/m^2 over 24 h recorded an overall response rate of 12.5%, with one complete and five partial responses.[21] Despite the use of G-CSF there was substantial grade 3 and 4 bone marrow toxicity, suggesting that for most patients the maximum tolerable dose had been achieved. A combination approach, however, of carboplatin and paclitaxel may result in enhanced activity and this remains to be tested in soft-tissue sarcomas.

This case illustrates a novel approach using an accelerated combination of carboplatin with paclitaxel. These agents have been used previously in a patient with advanced high-grade uterine leiomyosarcoma, achieving a good partial response.[20] The regimen used in this patient was part of a dose-intensification study,

with peripheral hematopoietic progenitor cell reinfusion and G-CSF support. Previous studies have clarified the necessary conditions for successful multicycle dose-intensified chemotherapy.[22] The carboplatin was administered with an AUC of 6, calculated using the Calvert formula,[23] and paclitaxel was prescribed at a dose of 175 mg/m^2 over 3 h. Apart from grade IV thrombocytopenia requiring platelet transfusions for a short period following her last cycle, she proceeded to consolidation pelvic radiotherapy without further problems. She remained well for 1 year post-diagnosis.

To the best of our knowledge, this is the first report in which a platinum drug has been used with a taxane in ESS producing a partial response. In conclusion, a combination of carboplatin and paclitaxel is effective in ESS, and requires further evaluation. The role of multicyclic, dose-intensive chemotherapy with PBPC mobilization using cytokines may also impact on response, but this question awaits randomized trials.[24]

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