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Short report

Remission of advanced uterine leiomyosarcoma with pulmonary metastases with carboplatin and paclitaxel

Andrzej P Kudelka, Wichai Termrungruanglert,[1] Saroj Vadhan-Raj, Creighton L Edwards, Datla G Varma, Carmen Tornos, Claire F Verschraegen and John J Kavanagh
The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Box 39, Houston, TX 77030, USA. Tel: (+1) 713 792-7959; Fax: (+1) 713 745-1541. [1]Chulalongkorn University Hospital, Bangkok, Thailand.

A patient who had a high-grade uterine leiomyosarcoma (LMS) with extensive intra-abdominal and pulmonary metastases at the time of diagnosis underwent supracervical hysterectomy, bilateral salpingo-oophorectomy and tumor reductive surgery. She then received induction chemotherapy with paclitaxel 135 mg/m^2 over 24 h and carboplatin (target AUC = 7.5 mg·ml/min) monthly for seven courses, achieving remission with a small amount of residual disease. The treatment was well tolerated except for peripheral neuropathy. Accordingly, the combination of carboplatin and paclitaxel may be considered in patients with advanced high-grade LMS of the uterus, and this regimen warrants further study in this disease.

Key words: Carboplatin, leiomyosarcoma, paclitaxel, pulmonary metastasis, uterus.

Introduction

Leiomyosarcomas (LMSs) of the uterus are rare tumors that account for approximately 25% of uterine sarcomas and 1–3% of all uterine malignancies.[1–5] The histological hallmarks of these tumors are an increased number of mitoses, cellular atypia and necrosis.[1,6] High-grade uterine LMSs have an extremely high malignant potential.[5,7] Although uterine LMS is usually confined to the uterus at the time of diagnosis, it is a highly lethal disease.[8–10] Five-year survival rates of 20–25% for patients with all stages of uterine LMS are reported.[4,5,9,10] The overall disease-free survival in stage I and II was 29% at 2 years. However, no long-term survival was observed in patients with extrauterine disease (stage III and IV) at the time of diagnosis.[11] The optimal therapy for a tumor limited to the uterus is total abdominal hysterectomy and bilateral salpingo-oophorectomy.[2,11] When disease is recurrent or advanced at the time of presentation, palliative surgery, radiation or chemotherapy may be attempted; however, these are often ineffective in controlling the disease.[11] Advanced or recurrent uterine LMS is usually treated with systemic chemotherapy.[5,11] Doxorubicin is the most active single agent, yielding response rates of up to 40%.[12] Other chemotherapeutic agents, including dimethyltriazenoimidazole (decarbazine), methotrexate, dactinomycin, cyclophosphamide, ifosfamide and cisplatin, have demonstrated response rates of 10–20% as single agents and up to 40% if combined with doxorubicin.[11–18]

We report the case of a patient who had an advanced stage uterine LMS with pulmonary metastases at the time of diagnosis. After initial surgery, the patient had remission of her tumor with a combination of carboplatin and paclitaxel. This is the first report of the use of carboplatin and paclitaxel as induction chemotherapy for advanced uterine LMS with pulmonary metastases.

Case report

A 59-year-old, gravida 0, para 0, white female presented at an outside institution complaining of a 1 month history of abdominal bloating, polyuria, urgency and dyspnea. On examination she was found to have a large pelvic mass. A preoperative chest X-ray on 29 June 1994 revealed bilateral multiple pulmonary nodules, consistent with metastatic disease. Computer tomography (CT) scan of the abdomen and pelvis revealed a large lobulated mass

Correspondence to AP Kudelka

in the pelvis, abutting the urinary bladder with areas of bladder wall involvement. There was evidence of metastatic left para-aortic retroperitoneal lymphadenopathy in the abdomen. On 30 June 1994, at the outside institution, she underwent exploratory laparotomy, supracervical hysterectomy, bilateral salpingo-oophorectomy and tumor reductive surgery. The peritoneal washings were positive for malignant cells. The pathologic findings revealed high-grade leiomyosarcoma of the uterus (Figure 1) with metastases involving the serosa of some small bowel loops. The tumor had more than 20 mitoses per 10 HPF, diffuse severe cytologic atypia and extensive necrosis. The patient's postoperative course was unremarkable and she was subsequently referred to our institution. She received induction chemotherapy with carboplatin and paclitaxel with the use of ossirene as a myelosuppression protector initially (four cycles) and then granulocyte colony stimulating factor (three cycles).[19] The patient received each cycle of chemotherapy with paclitaxel 135 mg/m^2 continuous i.v. infusion over 24 h on day 1 and after completion of paclitaxel infusion, carboplatin was infused over 1 h on day 2. The dose of carboplatin was calculated using Calvert's formula with a target AUC of 7.5 mg·min/ml.[20] She received this combination chemotherapy monthly for seven courses with one episode of neutropenic fever. She had a remarkable partial response, with resolution of the pulmonary metastases by chest X-ray (Figure 2) greater than 50% reduction of abdominal lymphadenopathy and approximately 90–95% reduction in the size of pelvic disease as documented on serial magnetic resonance imaging (MRI) in July and December 1994 (Figures 3 and 4). In February 1995, the patient developed moderate to severe sensory-motor peripheral neuropathy of both hands and feet. Follow up MRI of the abdomen and pelvis showed a plateau in response. Accordingly, the paclitaxel and carboplatin regimen was stopped.

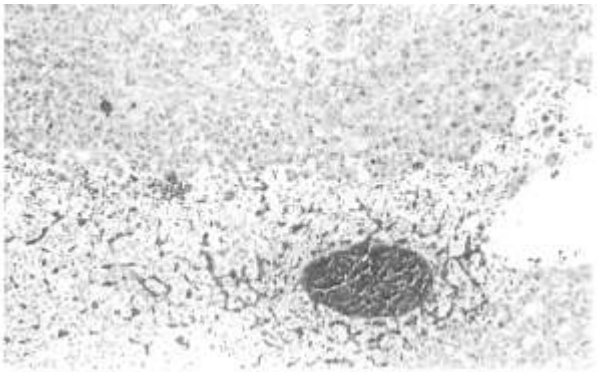

Figure 1. Photomicrogh showing LMS with mitosis and necrosis.

Discussion

The development of carboplatin, an analog of cisplatin, offered a potential advantage due to reduced non-hematologic toxicity. The predominant

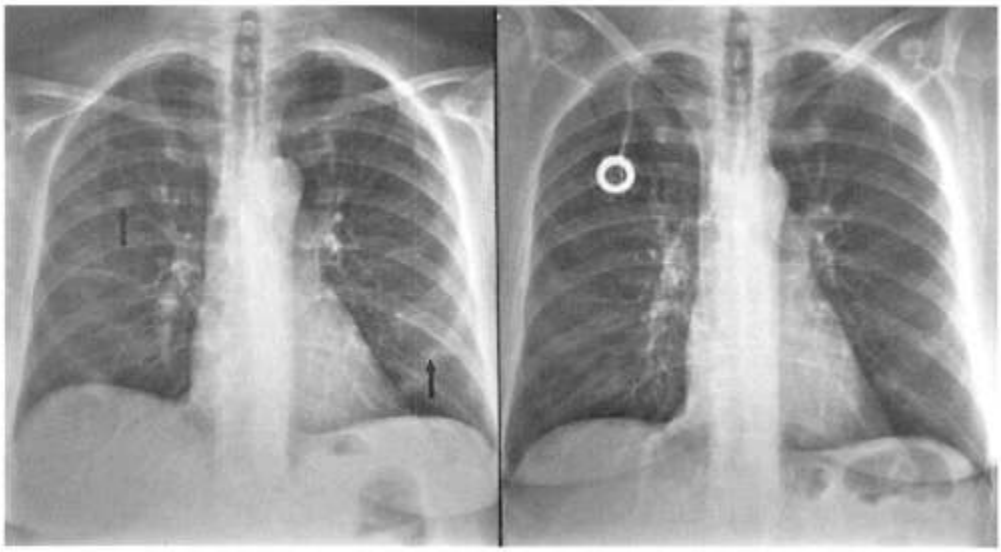

Figure 2. (Left) Chest X-ray on 13 July 1994 reveals bilateral metastatic lung nodules (arrows). (Right) Chest X-ray on 22 December 1994 reveals resolution of the lung nodules.

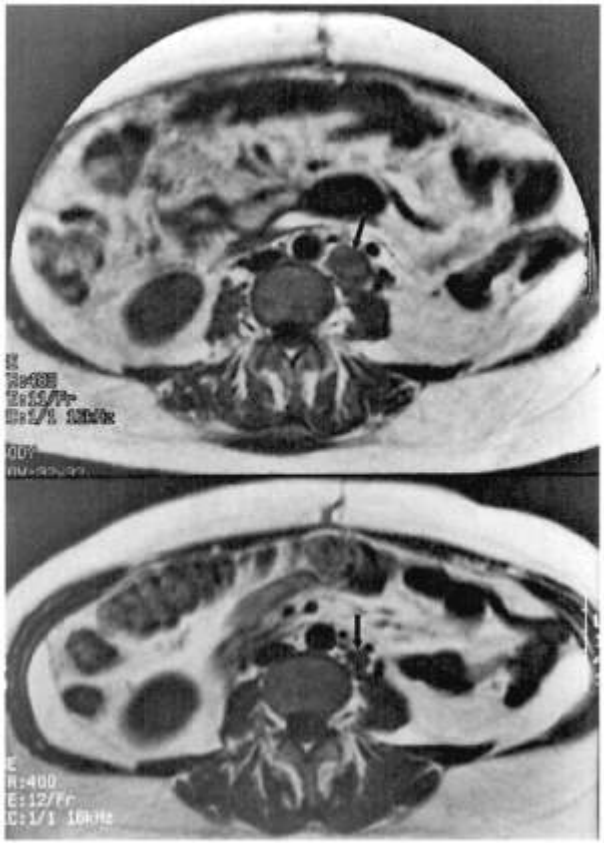

Figure 3. (Top) T1-weighted spin-echo abdominal MR scan on 14 July 1994 reveals enlarged metastatic paraaortic lymph node (arrow). (Bottom) Follow-up MR scan on 15 December 1994 reveals significant reduction in size of the node (arrow).

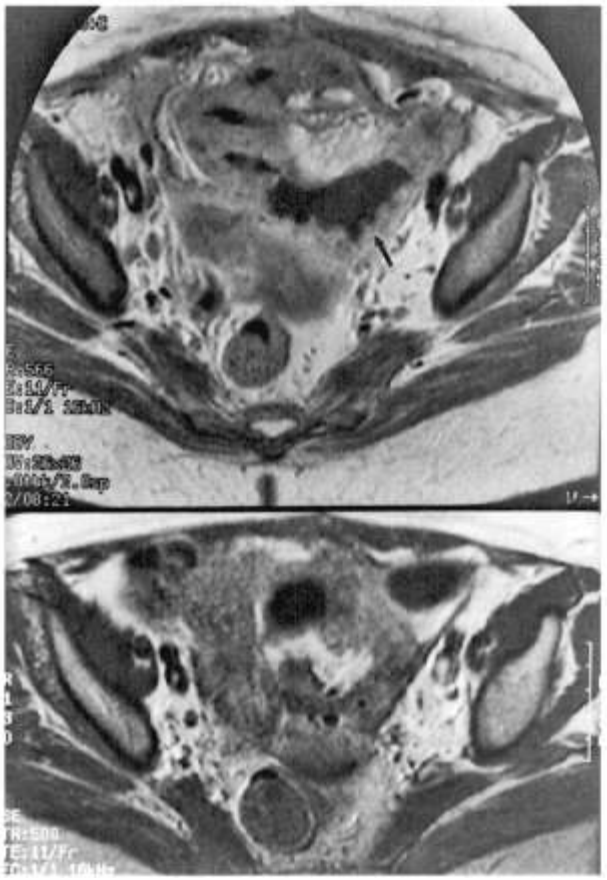

Figure 4. (Top) Intravenous contrast enhanced T1-weighted pelvic MR scan on 14 July 1994 reveals extensive pelvic disease involving multiple bowel loops with foci of necrosis identified (arrow). (Bottom) Follow-up MR scan on 15 December 1994 reveals marked resolution of disease.

data from clinical trials of advanced ovarian cancer have documented that carboplatin is equivalent to cisplatin in activity and causes considerably less ototoxicity, neurotoxicity and nephrotoxicity.[21,22] Carboplatin has also shown some activity in carcinomas of the endometrium and cervix.[23] In uterine sarcoma, Takada *et al.* report a case of remission of recurrent carcinosarcoma of the uterus with massive ascites with carboplatin.[24]

Paclitaxel, a taxane analog extracted from the bark of the western yew (*Taxus brevifolia*), attracted interest because of its unique mechanism of action. It promotes the polymerization of tubulin and inhibits the disassembly of microtubules.[25,26] Paclitaxel has shown antitumor activity in multiple clinical trials in cancers of the ovary, breast, head and neck, lung, and gastrointestinal tract.[27] In epithelial ovarian cancer, multiple phase II trials have demonstrated the antitumor activity of paclitaxel in both platinum refractory and advanced recurrent disease at various dose schedules.[28–30]

The apparent clinical non-cross-resistance between paclitaxel and cisplatin or carboplatin in other neoplasms, like ovarian and lung carcinoma, makes combinations which include these two agents of great interest.[25,31] A first-line study comparing the combination of paclitaxel plus cisplatin with cyclophosphamide plus cisplatin has reported superior overall and disease-free survival for the paclitaxel plus cisplatin arm.[32] The substitution of carboplatin in this regimen would have the advantage over cisplatin of decreased non-hematologic toxicity. The early report of the combination of carboplatin and paclitaxel have suggested that the degree of thrombocytopenia seen was less than that expected from the use of carboplatin as a single agent, raising the possibility of a beneficial interaction between the two drugs.[33] The tolerability and apparent efficacy of this combination in a phase I study of the Gynecologic Oncology Group in ovarian cancer[34] is

attractive for further evaluation in other malignancies as well.

In our case, at the time of diagnoses, the patient had lung metastases (stage IV disease) which is associated with an extremely poor prognosis. No long-term survival was observed in a study of 12 patients with extrauterine disease (stage III and IV) at the time of diagnosis. All the patients were dead of disease in less than 2 years.[11] Furthermore, the tumor in this patient demonstrated a very high grade LMS with more than 20 mitoses per 10 HPF. The patient received induction chemotherapy with paclitaxel and carboplatin post-operatively for seven courses which resulted in a partial response with minimal residual disease in the lungs and peritoneum.

The two main complications of this combination chemotherapy in our case were one episode of neutropenic fever and progressive peripheral neuropathy. Langer *et al.* report a 13% incidence of neutropenic fever in patients with the same dose-schedule as in our case.[35] Overall, 45% experienced grade 4 neutropenia. Thrombocytopenia was relatively mild. Peripheral neuropathy had affected at least 38% of patients. However, neuropathy caused only one patient to cease study therapy and otherwise did not require dose attenuation. In a study of Shea *et al.* in patients with unresectable or metastatic cancer, the most frequent serious non-hematologic complication was peripheral neuropathy.[36] Two out of 26 cases experienced grade 3 motor weakness with foot drop. Milder sensory-motor neuropathy with paresthesias and fine motor incoordination were observed in four patients. These symptoms persisted in all patients, but slowly improved over 4–6 months.

Conclusion

This is the first report of remission with carboplatin and paclitaxel of an advanced uterine LMS with pulmonary metastases. The patient tolerated this combination chemotherapy reasonably well except for peripheral neuropathy. Further studies of the combination of carboplatin and paclitaxel in patients with uterine LMS are warranted.

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