Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer

A. Lissoni, G. Zanetta, G. Losa, A. Gabriele, G. Parma & C. Mangioni
Department of Obstetrics and Gynecology, S. Gerardo Hospital, III branch of University of Milan, Monza, Italy

Summary

Objective: to evaluate the antitumour activity of paclitaxel in patients with endometrial cancer pretreated with cisplatin, doxorubicin and cyclophosphamide (PAC).

Materials and methods: Eligible patients had complete initial surgery, expected survival >3 months, performance status <1, measurable or evaluable disease. Paclitaxel was given over three hours at the dose of 175 mg/m², repeated every 3 weeks. Tumour response was first evaluated after 3 cycles. A maximum of 10 cycles was given in responders.

Results: 19 patients entered the study and a total of 105 cycles were administered. Complete and partial responses were achieved in 2 and 5 patients, respectively, for an overall response rate of 37% (95% CI: 16%–62%). The response rate in patients refractory to platinum was 22%. One patient is alive without evidence of disease 16 months after the start of treatment. The most common side effects were mild to moderate myalgia and peripheral neuropathy, which occurred in 31% and 47% of patients, respectively. In only 1 patient treatment had to be discontinued because of severe myalgia.

Conclusion: Paclitaxel is active in patients with endometrial cancer pretreated with PAC. Further studies with paclitaxel incorporated in the initial treatment for advanced disease are warranted.

Key words: chemotherapy, cisplatin, endometrial cancer, paclitaxel, survival

Introduction

In developed countries endometrial cancer is the most common malignancy of the genital tract [1]. The majority of cases may be cured by surgery, but in the event of recurrence long-term survival is still uncommon, except in the few patients in whom a complete surgical resection or radical irradiation of small tumor burden is possible. Doxorubicin [2, 3] and cisplatin [4] are the most effective drugs in advanced or recurrent endometrial cancer and response rates of up to 42% have been reported. The use of cisplatin, doxorubicin and cyclophosphamide in combination (PAC regimen) has been associated with a response rate between 40% and 60% [5, 6] and in several countries this regimen is currently the standard salvage therapy for patients in whom local treatment with surgery or irradiation is inappropriate.

Paclitaxel is a new and promising antitumour agent for which an objective response rate of up to 37% [7–9] has been reported in patients with ovarian carcinoma pretreated with platinum compounds. The common origin of ovarian and endometrial epithelium in the Mullerian tissue provided the rationale for evaluating the antitumour activity of paclitaxel in endometrial cancer.

In a phase II study of the GOG, paclitaxel, given at 250 mg/m² over 24 hours every 3 weeks, produced an overall response rate of 35% in 28 patients without prior chemotherapy for metastatic disease [10].

This paper reports the results of a phase II study of paclitaxel in patients with endometrial cancer failing on or relapsing after first line therapy with PAC regimen.

Materials and methods

From May 1993 to July 1995, 19 consecutive patients (pts) with a mean age of 61 years (range: 46 to 75), histological diagnosis of endometrial carcinoma, either adenocarcinoma (18 pts) or adenosquamous (1 pt), and measurable or evaluable disease not suitable for surgery or radiotherapy entered the study.

Eligibility criteria also included a life expectancy of at least 3 months, performance status >1, complete initial surgery (including at least total abdominal hysterectomy with bilateral salpingo-oophorectomy), prior chemotherapy with cisplatin, doxorubicin and cyclophosphamide (PAC), given either as postoperative (10 pts), neoadjuvant (2 pts), or as salvage treatment in the event of recurrence (7 pts). According to the criteria proposed by Markman and Hoskins for ovarian cancer [11], 9 patients were considered platinum-resistant (with progression or no change of disease in 7 and development of new lesions within six months from the end of adjuvant chemotherapy in 2), 3 patients were potentially platinum sensitive, while 7 were not evaluable for response to PAC, which had been given as adjuvant therapy more than 12 months before the start of paclitaxel.

Six patients received prior irradiation, given as adjuvant treatment in 4 and as salvage in 2. Initial tumour stage was I in 8 cases, II in 1, III in 7 and IV in 2. Tumor parameter was located in the pelvis in 4 patients, extrapelvic sites in 13 (lung in 6, liver in 1, nodes in 6) and
in both pelvic and extrapelvic sites in 2. In only 1 patient was the tumour site within the irradiation field.

Baseline evaluation included physical exam with pelvic examination, hematology, complete chemistry, electrocardiogram, chest X-rays and tumour evaluation by CT, US or NMR.

Paclitaxel was given at the dose of 175 mg/m² over three hours. One hour before the administration of paclitaxel, patients were premedicated with hydrocortisone (250 mg i.v.), chlorphenamine (10 mg i.m.) and cimetidine (300 mg i.v.). Complete blood cell counts were repeated weekly. Treatment was repeated every 3 weeks if the granulocyte count was >1.5 10⁹/μl; if it was lower treatment was delayed by one week.

Pelvic examination was performed before each cycle. In the absence of clinical evidence of tumour progression, at least 3 cycles were given before tumour evaluation by diagnostic imaging was repeated.

Response and toxicity were defined according to WHO criteria [12]. Patients showing an objective response received 3 further cycles of treatment and then, if still in response, continued treatment for a total of 10 cycles. Patients in complete or partial remission after 10 cycles did not receive any additional chemotherapy. In patients showing stable disease after the first 3 cycles further treatment was left to the discretion of the investigator.

Follow-up procedures with pelvic examination and vaginal cytology were performed one month after the end of paclitaxel and then every two months. In patients with complete response, abdominopelvic US or CT scan were performed every 3 months.

The duration of partial response was calculated from the start of treatment until the documentation of tumour progression; the duration of complete response was calculated from the moment the complete response was documented.

Survival was defined as the time interval between entry into the study to death, or to the date of the last contact.

Results

A total of 105 courses was given, with a median number of 6 cycles. Of 19 patients entered, 3 discontinued treatment after 3 cycles because of tumour progression, 9 had stable disease and 7 showed an objective response, which was complete in 2 cases, for an overall response rate of 37% (95% CI: 16%–62%). Complete responses lasted 10 and 16+ months, respectively. The median duration of partial response was 7 months (range: 6–12 months) and the median survival of responders was 14+ months (range: 4–17+). None of the 9 patients with stable disease after three cycles achieved an objective response after 3 additional cycles.

When analysed according to previous response to platinum, objective remissions were reported in 2 of 9 patients resistant to platinum (22.2%), in none of 3 patients with platinum potentially sensitive tumors, and in 5 (71%) of 7 whose response to platinum was not evaluable.

One patient, who started progestins while she was showing a complete response in lung lesions and a partial response in groin nodes, is still alive without evidence of recurrence 16 months after the start of the chemotherapy.

Subsequent treatment in patients progressing on or relapsing after paclitaxel consisted of hormones in 10 cases, palliative excision of lung metastases in 1, palliative irradiation in 4 and different chemotherapy in 3.

Toxicity

Mild to moderate myelotoxicity was reported in 89% of patients; 2 patients developed uncomplicated grade 3 neutropenia (Table 1). Neither treatment delays nor dose reductions because of myelotoxicity were performed and significant differences in myelotoxicity between patients with/without a previous radiotherapy were not reported. Six patients (31%) suffered from arthralgia and myalgia which were of moderate degree in all but 1 patient, who required treatment discontinuation after 3 cycles. Mild to moderate peripheral neuropathy, consisting mainly of reversible paresthesias, occurred in 47% of patients. Three patients complained of itching, controlled by chlorphenamine, the days following the treatment. Total alopecia was universal.

Table 1. Worst toxicity in 19 patients.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Number of patients with toxicity</th>
<th>WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Discussion

The results of this study, with 7 responses among 19 patients pretreated with PAC and an overall response rate of 37%, confirm the preliminary report of the GOG and suggest that paclitaxel is an effective agent in endometrial cancer. Other relevant features were the observation of objective responses (22%) in tumours refractory to cisplatin, the inducement of long-lasting complete responses and the limited toxicity of the treatment, which can be proposed also for patients pretreated with chemo-radiotherapy and for prolonged periods of treatment.

The use of a 3 hr infusion and of a conventional dose of 175 mg/m² simplifies the administration of paclitaxel and renders it suitable for inclusion in multi-drug regimens. The most promising combinations include paclitaxel, one anthracycline, possibly the less cardiotoxic analog epirubicin, and cisplatin at the dose of 50 mg/m², as in the PAC regimen. A phase II study with this combination in patients with locally advanced or metastatic disease not pretreated with chemotherapy has already been started by our group.
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References


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Correspondence to:
Gerardo Zanetta, MD
Gynecologic Surgery
Eisenberg 5A, Mayo Clinic
200 1st Street S.W.
Rochester, MN 55905, USA