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

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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 tu-
mour site within the irradiation field.

Baseline evaluation included physical exam with pelvic examination,
haematology, 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 pre-
medicated 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 > 1.5 10³/µl; if it was lower treatment was
delayed by one week.

Pelic examenation was performed before each cycle. In the ab-

cence 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 pa-
tients 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, abdomino-
pelvic 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 dura-
ton of complete response was calculated from the moment the com-
plete 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 re-
sponse, 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 re-
sponders 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 pa-
tients 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 par-
tial response in groin nodes, is still alive without evi-
dence 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, pallia-
tive 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 per-
formed and significant differences in myelotoxicity be-
tween 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 discon-
 tinuation after 3 cycles. Mild to moderate peripheral
neuropathy, consisting mainly of reversible pares-
thesias, 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 toxicitiy WHO grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>2</td>
</tr>
<tr>
<td>Itching</td>
<td>1</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 induction of long-lasting
complete responses and the limited toxicity of the treat-
ment, which can be proposed also for patients pretreat-
ed 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 in-
clude 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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