Esorubicin in advanced endometrial cancer: an ineffective and potentially toxic therapy

A Southwest Oncology Group study

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Summary

The Southwest Oncology Group conducted a phase II study of esorubicin treatment in patients with advanced endometrial cancer who had received no prior chemotherapy. Twenty of 31 patients were fully evaluable for response and toxicity. There were no clinical responses to treatment and 60% (12/20) of the patients developed severe or life threatening leukopenia on therapy. One evaluable patient was removed from study after a cumulative dose of 150 mg/M² due to a reduction in left ventricular ejection fraction on MUGA scan and another developed congestive heart failure several months after discontinuation of treatment. Esorubicin has significant toxicity and limited clinical activity in patients with advanced endometrial cancer.

Introduction

Locally recurrent or metastatic endometrial cancer remains a difficult clinical problem despite anti-tumor responses in some patients to progestational agents or chemotherapy [1,2]. However, no single agent or combination has emerged as the treatment of choice. Based on its encouraging in vitro activity, [3] the Southwest Oncology Group investigated the effectiveness of the doxorubicin derivative Esorubicin (4’ deoxydoxorubicin) in patients with advanced endometrial carcinoma.

Materials and methods

Patient selection

Patients with measurable metastatic or locally recurrent endometrial carcinoma were eligible for study if they had recovered from prior radiotherapy, had been off hormonal therapy for at least three weeks, and had received no prior chemotherapy.

Treatment plan and evaluation

Patients less than age 65 with no history of prior pelvic irradiation (good risk patients) received Esorubicin in a dose of 30 mg/M² every 21 days by rapid IV administration. The dose was reduced to 25 mg/M² in other patients. Treatment was delayed on a weekly basis until recovery of the WBC count to >3000/µl and the platelet count to >100,000/µl. Dose modifications are outlined in Table 1. Physical exam and appropriate scans and
Table 1. Esorubicin dose levels and modifications

<table>
<thead>
<tr>
<th>Dose levels (MG/M²)</th>
<th>Starting dose</th>
<th>*+1</th>
<th>*+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>−2</td>
<td>−1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good risk</td>
<td>15.0</td>
<td>30.0</td>
<td>32.5</td>
</tr>
<tr>
<td>Poor risk</td>
<td>12.5</td>
<td>18.75</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Dose modifications (Based on nadir counts)

<table>
<thead>
<tr>
<th>Absolute granulocytes/µl</th>
<th>Platelets/µl</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1500</td>
<td>&gt;100,000</td>
<td>Full</td>
</tr>
<tr>
<td>1000−1500</td>
<td>75,000−99,000</td>
<td>−1</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>50,000−74,000</td>
<td>−2</td>
</tr>
</tbody>
</table>

* Dose increased every 2 courses of therapy if granulocytes > 2000/µl and platelets > 100,000/µl on day of treatment.

X-rays were used for serial tumor measurement. Standard SWOG criteria were used to assess toxicity and response.

**Toxicity**

Severe or life treating leukopenia (WBC counts 1000−2000/µl or less than 1000/µl respectively) was seen in 12 of the 20 evaluable patients (60%). Thrombocytopenia was much less evident with only 3 of 20 patients (15%) showing a decrease in the platelet count to below 100,000/µl during therapy. Ten of 20 patients experienced nausea and vomiting with treatment. Alopecia was not meticulously recorded but when noted was moderate or severe in 5 to 7 patients. Nail discoloration, phlebitis at the injection site, rash, and pruritis were noted in one patient each. One patient was removed from study after a total Esorubicin dose of 365 mg (150 mg/ M²) due to a decrease in cardiac ejection fraction to 34% on MUGA scanning. A second patient, who received a total dose of 400 mg (200 mg/M²) prior to progressive disease, developed congestive heart failure several months after discontinuation of Esorubicin.

**Results**

**Patient characteristics, response and survival**

Thirty-one patients were entered into the study. Ten of the 31 were ineligible and 1 was ineligible leaving 20 patients fully evaluable for response, toxicity, and survival. Seven of the 10 ineligible patients were excluded based on pathology review and 3 had not been off hormones for at least 3 weeks. The one ineligible patient refused therapy after entry into the study. Thirteen of 20 evaluable patients had distant metastatic disease and 7 had only pelvic or abdominal spread. Eighteen patients had received prior radiation and 8 had been treated with hormones.

The 20 evaluable patients received a mean of 3.8 courses of therapy and a mean total Esorubicin dose of 152 mg. No responses were seen in the 20 evaluable patients. Survival ranged from 18 to 772 days with a mean of 154 days.

**Discussion**

We are unenthusiastic about further clinical studies utilizing Esorubicin in the treatment of advanced endometrial cancer. No response in 20 evaluable patients (95% confidence interval 0 to 17%) suggests a lower level of activity than Doxorubicin [4]. In addition, Esorubicin produced severe leukopenia, significant nausea or vomiting, and alopecia in the majority of patients in our study. Despite early evidence that Esorubicin appeared to cause little cardiac dysfunction, [5] fatal cardiomyopathy has recently been reported [6]. This study did not allow us to quantitate the effect of treatment of cardiac function, but the one case of reduction in ejection fraction and the delayed onset of congestive heart failure in a second patient are cause for concern. We conclude that Esorubicin will have little clinical utility in the treatment of endometrial cancer.