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The Gulf Journal of Oncology

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Docetaxel In Advanced Or Metastatic Endometrial Cancer: Clinical Outcome (Mansoura University)

R.H. Hamed¹, S.A. Elkhalk¹, S. Roshdy²

¹Clinical Oncology and Nuclear Medicine Department, ²Mansoura Oncology Center, Faculty of Medicine, Mansoura University, Egypt

Abstract

Background and Objectives

The aim of this study was to evaluate the efficacy, safety and toxicity of docetaxel as first line chemotherapy or previously treated patients (one regimen) in patients with recurrent or metastatic endometrial cancer.

Patients and Methods

Prospective phase II, in patients referred to the Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Mansoura University, Egypt.

Fifty patients with advanced or metastatic endometrial cancer were enrolled to receive docetaxel 70 mg/m² administered intravenously on day 1 of a 3-week cycle. If patients responded well to docetaxel, additional cycles were administered until progressive disease or unacceptable toxicity occurred. Therapy response was evaluated every 6-week.

Results

Fifty patients with a median age of 60 years (range, 40–70 years) who entered the study, 17 patients (34%) had received one prior chemotherapy regimen. All patients were evaluable for efficacy, yielding an overall response rate of 34% (95% confidence interval, 14.8–55.6%); complete response and partial response (PR) were 4 and 30%, respectively. Of the 17 pre-treated patients, five (29%) had a PR. The median duration of response was 2 months. The median time to progression was 4 months and the median survival time was 18 months. The predominant toxicity was grade 3–4 neutropenia, occurring in 92% of the patients, although febrile neutropenia arose in 92% of the patients, although febrile neutropenia arose in 92% of the patients. Oedema was mild and infrequent.

Conclusion

This prospective phase II trial clearly demonstrated that docetaxel is active in the treatment of endometrial cancer. Toxicity was manageable and predominantly haematologic.

Keywords

Docetaxel, advanced or metastatic endometrial cancer, phase II

Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the world and the seventh most common cause of death from cancer in women in western Europe¹. The median age at diagnosis is the sixth decade, with abnormal uterine bleeding at the presentation in 90% of the patients². While early-stage endometrial cancer typically responds well to standard therapies, low survival rates for advanced or recurrent disease result from limited and ineffective chemotherapy and hormonal treatment options. The American Cancer Society estimates that 15 percent, or three out of every 20 of women with stage IV endometrial cancer, will survive more than five years.³

Cytotoxic chemotherapy is the mainstay of therapy for metastatic endometrial carcinoma. Many cytotoxic chemotherapy regimens have demonstrated activity. Response rates, however, are modest, with progression free intervals of approximately 4 to 6 months and median overall survival in the range of 12 months.⁴ Many

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women with metastatic endometrial cancer are elderly and may have previously undergone pelvic radiation therapy, making them more susceptible to adverse effects of aggressive cytotoxic regimens.\(^{(5)}\)

The taxanes, paclitaxel and docetaxel, are potent chemotherapeutic agents that block tubulin depolymerisation, leading to the inhibition of microtubule dynamics, and have significant clinical efficacy for various solid tumors. Paclitaxel has been evaluated as an active agent for endometrial cancer.\(^{(6)}\) However, preclinical data show that docetaxel has increased potency and an improved therapeutic index compared with paclitaxel \(^{(7)}\) and its short 1-h infusion time offers a substantial clinical advantage over the prolonged infusion durations required with paclitaxel. Docetaxel and paclitaxel also have substantially different toxicity profiles. In particular, docetaxel has a significant lower incidence of neurotoxicity in comparison to paclitaxel.\(^{(8)}\)

There is limited reported experience with use of docetaxel in endometrial cancer, but objective clinical activity has been demonstrated in a range (approximately 30% response rate) comparable with that documented with single-agent paclitaxel.\(^{(9)}\) The weekly administration of docetaxel in metastatic endometrial cancer has also been shown to be reasonably well tolerated and to result in objective clinical responses (20% response rate).\(^{(10)}\)

In this study we evaluate the clinical efficacy and tolerability of docetaxel in patients metastatic and recurrent endometrial cancer.

**Patients and Methods**

**Eligibility criteria**

Patients were enrolled at Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital. The eligibility criteria for the patients in this study were as follows: age between 20 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, primary lesion histologically confirmed to be endometrial carcinoma; International Federation of Gynecology and Obstetrics (FIGO) stage III, stage IV, or recurrent cancer; maximum measurable diameter at computed tomography (CT) or magnetic resonance imaging at least 20 mm; or a maximum measurable diameter at helical CT of at least 10 mm. Patients were either chemotherapy-naive or had received one prior chemotherapy regimen for endometrial cancer, with 4 weeks between prior therapy and study treatment. Prior treatment with a taxane was not allowed. Adequate organ function was required for study entry: neutrophil count greater than 2000/mm\(^3\), platelet count greater than 100,000/mm\(^3\), serum bilirubin, SGOT, SGPT, serum creatinine within normal limit and normal electrocardiogram. No other history of active malignancy and no other serious medical disease. Written informed consent was obtained from all patients before registration.

**Treatment schedule**

Docetaxel 70 mg/m\(^2\) was infused over a 1–2 h period. The treatment was repeated every 3 weeks unless there was documented disease progression or unacceptable toxicity. To prevent docetaxel-related hypersensitivity or fluid retention, patients received premedication with six doses of corticosteroids—each equivalent to 50 mg of prednisolone—starting 12 hours before and ending 18 hours after the docetaxel infusion. Antiemetics were prescribed routinely before each cycle. If any adverse events listed below were seen during treatment in the previous cycle, the dose for the subsequent cycle was to be reduced by 10 mg/m\(^2\) in the following instances: occurrence of febrile neutropenia, grade 4 neutropenia persistent for at least 5 days, grade 4 thrombocytopenia, bleeding tendency due to grade 3 thrombocytopenia, and platelet transfusion, or if a patient experienced any grade 3-4 non haematologic toxicities except nausea, vomiting, anorexia, fatigue, alopecia or hypersensitivity. In case of febrile grade 3 neutropenia or grade 4 neutropenia, the administration of G-CSF was permitted. Treatment was restarted when the neutrophil count was >1500 /mm\(^3\), platelet count >100 000 /mm\(^3\), AST/ALT/ALP levels <2.5 times ULN, and neuropathy or oedema <grade 1.
Response evaluation

The tumor response was assessed after 2 cycles of docetaxel according to the standard RECIST criteria. Target lesions included all measurable lesions. Complete response (CR) was defined as the complete disappearance of all target and non-target lesions, with no development of new disease. Partial response (PR) was defined as a reduction by >30% in the sum of the longest diameter of target lesions. Complete response or PR was confirmed by repeat assessments performed no less than 4 weeks after the criteria for response were first met. The response rate was defined as a total of complete response and partial response. Progressive disease (PD) was defined as an increase by >20% in the sum of the longest diameter of all target lesions, or the appearance of one or more new lesions and/or unequivocal progression of existing, non target lesions. Stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for a PR, nor sufficient increase to qualify for PD. All tumors were radiographically assessed for response every 6 weeks.

Toxicity evaluation

Toxicities were classified and evaluated by grade in accordance with the National Cancer Institute–Common Toxicity Criteria (Version 2).

Statistical analysis

The primary end point was the response rate, and the secondary endpoints were the frequency of toxicities, and progression-free survival (PFS). Using this design with 50 patients, we had a statistical power of 80%, at a significance level of 0.05 to detect a 30% response rate. The response rate was defined as a total of complete response and partial response. The progression-free survival (PFS) was defined as the time from the first medication to the date of a PD event or death (due to endometrial cancer or study drugs). Overall survival (OAS), defined as time from diagnosis to death (including deaths with or without recurrence) or last follow up for those who were still alive. The PFS and OAS rates were calculated by the using the Kaplan–Meier method. Statistical analysis was performed using a commercially available software package (SPSS for Windows 15; SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

From April 2008 to October 2011, 51 patients were enrolled on this study. Data of one patient who did not receive treatment was deleted from the study. A total of 50 patients were analyzed and evaluated for response, toxicity, and survival.

Baseline characteristics of patients were listed in (Table 1). The median age was 60 years, ranging from 40 to 70 years. The Eastern Cooperative Oncology Group performance status at presentation was 0 in 30 patients and 1 in 18 patients and only 2 patients (4%) had performance status 2. Recurrent disease was predominant representing 78%. Grade II was the most common grade representing 40%. Several patients had unfavorable histologic characteristics: adenosquamous features (three) and uterine papillary serous cancers (two). Most patients (90%) had undergone total abdominal hysterectomy and bilateral salpingoophorectomy, and one-half of patients had prior radiotherapy. Of those patients who received prior chemotherapy (17), 11 received combination
doxorubicin-platinum in combination, six received platinum alone.

**Treatment Characteristics**

The median number of docetaxel cycles received by patients was six (range, 2-10). Nine patients (18%) experienced dose reductions for the following reasons: Five patients experienced febrile neutropenia and four patients had non-haematologic toxicities, diarrhea (occurred in two patients) and neuropathy (occurred in two patients).

The most frequent reason for patients not receiving chemotherapy was patient refusal secondary to toxicity. Three patients terminated the study as a consequence of the following toxicities: grade 4 hypersensitivity reaction despite premedication with dexamethasone (two), infection associated with grade 3-4 neutropenia (two), and grade 3 oedema with pleural effusion after six treatment cycles (one).

**Response**

(Table 2) presents the assessment of response to treatment. The overall response rate (ORR) was 17 of 50 patients, 34% (95% CI, 14.8–55.6%). Of the 17 patients who had prior chemotherapy, five (29%) achieved a PR: three had received doxorubicin-platinum and two had received platinum alone. The histologic analysis revealed responses among the following tumor types: endometrioid adenocarcinoma (13 of 45 patients), squamous differentiated adenocarcinoma (2 of 3), papillary serous (2 of 2) and undifferentiated cancer (1 of 1). The median time for the onset of effect was 2.5 months (range, 0.5–5.5) and the median duration of response was 2 months (range, 1-5). The median follow up time was 18 months (range, 2-40) and median PFS was 4 months (95% CI, 2-10 months) (Figure 1). Median survival time was 18 months (95% CI, 8-24 months).

**Treatment Toxicity**

In all, 50 patients were assessable for toxicity (Table 3). The major adverse events were hematological toxic effects. Neutropenia was seen in nearly all patients, 46 (92%) patients experienced grade 3 or 4 neutropenia, and five (10%) developed febrile neutropenia, infection associated with grade 3-4 neutropenia was reported in two patients. Non-haematologic toxicities included grade 3 or 4 anorexia and nausea and/or vomiting experienced by some.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Age (yr), Median (range)</td>
<td>60(40-70)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (60)</td>
</tr>
<tr>
<td>1</td>
<td>18(36)</td>
</tr>
<tr>
<td>2</td>
<td>2(4)</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
</tr>
<tr>
<td>Stage III, IV Recurrent</td>
<td>112(22)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Endometrioid Adenocarcinoma with squamous differentiated Papillary serous</td>
<td>45(50)</td>
</tr>
<tr>
<td>3(6)</td>
<td></td>
</tr>
<tr>
<td>2(4)</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>18 (36)</td>
</tr>
<tr>
<td>II</td>
<td>20(40)</td>
</tr>
<tr>
<td>III</td>
<td>12(24)</td>
</tr>
<tr>
<td><strong>Prior treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>45(50)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>25(50)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>5(10)</td>
</tr>
<tr>
<td><strong>Prior chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>33(66)</td>
</tr>
<tr>
<td>Doxorubicin and platinum</td>
<td>11(22)</td>
</tr>
<tr>
<td>Platinum alone</td>
<td>6(12)</td>
</tr>
</tbody>
</table>

**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Response</th>
<th>patients received prior chemotherapy (17 patients)</th>
<th>Patients didn’t receive prior chemotherapy (33 patients)</th>
<th>Total (50 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>5</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>35</td>
<td>9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>ORR</td>
<td>5</td>
<td>29</td>
<td>12</td>
</tr>
</tbody>
</table>

ORR=overall response rate.

**Table 2: Response (RECIST criteria) to docetaxel**
patients (20% and 8%, respectively). Other grade 3 gastrointestinal adverse events that occurred at high frequency were diarrhea and constipation (4% and 12%, respectively). Grade 3 motor neuropathy occurred in one patient (2%), and sensory neuropathy occurred in two patients (4%).

Three patients terminated the study as a consequence of the following toxicities: grade 4 hypersensitivity reaction despite premedication with dexamethasone (two), infection associated with grade 3–4 neutropenia (two), and grade 3 oedema with pleural effusion after six treatment cycles (one). All three patients recovered after receiving recommended medical treatment. There was no treatment-related death.

**Discussion**

Endometrial cancer is the most common gynecologic cancer. The mainstay of treatment of recurrent and metastatic endometrial cancer remains systemic therapy in the form of hormonal therapy or cytotoxic chemotherapy. There have been a few prospective trials designed to study the feasibility and efficacy of systemic chemotherapy in advanced cases of endometrial cancer. Patients with low-grade disease with estrogen receptor (ER)-positive and progesterone receptor (PR)-positive carcinoma tend to respond as well to hormonal therapy as to cytotoxic chemotherapy, with fewer side effects. Hormonal therapy may also be prioritized in patients with poor performance status and/or multiple medical comorbidities. Cytotoxic chemotherapy may be more appropriate as initial therapy for younger patients with high grade disease. Cisplatin plus doxorubicin was the standard of care for many years but the response has been mostly only partial with short duration. Because of the low benefit of prior treatments, trials with new chemotherapeutic agents are strongly needed.

Taxanes have shown activity in this setting previously, with paclitaxel demonstrating overall response rates of 27–37% when used as a single agent in endometrial cancer. In our study, ORR was 34%, CR 4%, PR 30% and stable disease in 30% while 36% had progressive disease. The median PFS was 4 months and median survival 18 months. Of 17 pre-treated patients, five (29%) had a PR, suggesting that it is active as second-line therapy too. Katsumata N, et al had similar findings in their conducted trial of docetaxel in 32 patients with advanced and metastatic endometrial cancer and the ORR was 31% (11 patients); complete response and partial response (PR) were 3 and 28%, respectively. Of 13 pretreated patients, three (23%) had a PR. The median time to progression was 3.9 months. Median survival time was 17.8 months.

Combination chemotherapy with paclitaxel and carboplatin or cisplatin has resulted in response rates of 50–56%. However, a GOG phase III trial in endometrial cancer compared cisplatin plus doxorubicin to doxorubicin, cisplatin, and paclitaxel with granulocyte colony-stimulating factor (G-CSF) support. The three-drug arm produced more objective responses than the two-drug arm (57% vs. 34%, P < .01). Progression-free survival was extended to 8.3 months compared with 5.3 months in the control arm (P < .01); and overall survival reached a median of 15.3 months compared with 12.3 months (P
However, more grade 3 neuropathy (12 vs. 1%) and congestive heart failure were observed with three-drug combination than with two-drug combination. \( ^{(15)} \) As seen in previous trial, increasing efficacy with more chemotherapy also led to increasing toxicity; patients receiving the three-drug combination were more likely to suffer congestive heart failure and grade 3 and 4 neurotoxicity. In view of this imbalance between efficacy and toxicity, the three-drug combination has not been accepted as the standard chemotherapy regimen in routine clinical practice. Attarian H, et al. study assessed carboplatin plus paclitaxel in patients with advanced locoregional recurrence and metastatic endometrial cancer, the ORR was 54% (16 out of 30), CR in 13% and PR in 40%. The median progression free survival was 8.2 months. The 6 months overall survival was seen in 80% of the patients.\(^{(21)}\) In previous trial of combination chemotherapy, ORR and PFS were superior to our results as we used single agent but we reported low rates of serious toxicities and better OAS. These toxicities were manageable and predominantly haematologic.

Docetaxel has a toxicity profile that is different from paclitaxel. In particular, neurotoxicity occurs at a low incidence with docetaxel. In current study, 92% of patients developed neutropenia (grade 3 and 4), 10% had febrile neutropenia, only one patient developed grade 3 motor neuropathy and 4% developed grade 3 sensory neuropathy recovered in several weeks. Only one patient developed pleural effusion and grade 3 oedema since the routine premedication with corticosteroids was not applied.

### Conclusion

This prospective phase II trial, although relatively small in sample size, clearly demonstrated that docetaxel is active in the treatment of endometrial cancer. Toxicity was manageable and predominantly haematologic. The exploration of the efficacy of docetaxel combinations for the treatment of endometrial cancer is of great interest and will be initiated.

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1. N. Colombo, E. Preti, F. Landoni; et al. Endometrial cancer: esmo clinical practice guidelines for diagnosis, treatment and follow-up


