Results of cisplatin, adriamycin and etoposide chemotherapy in patients with recurrent and metastatic endometrial cancer

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Summary

The efficacy of the combination treatment of cisplatin, adriamycin and etoposide were retrospectively evaluated in 26 recurrent or metastatic endometrial cancer patients. One hundred and twenty-three treatment courses were observed. Patients received 20 mg/m^2 cisplatin and 80 mg/m^2 etoposide by continuous IV infusion for three days and adriamycin 40 mg/m^2 IV the second day. Treatment courses were repeated every four weeks. Megestrol acetate, 160 mg/day, was added in six patients who had positive progesterone receptors. Ten (38.5%) women had complete and three (11.5%) patients had partial response with an overall response rate of 50%. Median follow-up was 24 months. Surviving patients were alive for four months and six years. Toxicity was mainly hematological and gastrointestinal ulcerations and stomatitis were also observed.

Key words: Endometrial cancer; Chemotherapy; Cisplatin; Adriamycin; Etoposide.

Introduction

Most endometrial cancer patients are effectively treated by surgery and/or radiation. Systemic treatment is required in patients with initial advanced disease or at the time of relapse. Cisplatin and adriamycin are the most effective drugs with response rates ranging from 20 to 35% [1]. Higher response rates around 50% have been observed for the combination of these drugs [2]. A combination of adriamycin, etoposide, 5-fluorouracil and cisplatin was reported to have a 41% response rate and a median survival duration of 14 months [3]. Patients who received a combination of cisplatin, etoposide, adriamycin and megestrol acetate were reported to have longer survival when compared to women who received a combination of melphalan, 5-fluorouracil and medroxyprogesterone acetate [4]. We retrospectively analysed the cases of advanced or recurrent endometrial cancer that were treated with the combination of cisplatin, adriamycin and etoposide.

Materials and Methods

Cisplatin, adriamycin and etoposide chemotherapy was started in 26 consecutive documented recurrent and/or metastatic endometrial cancer patients. A total of 123 treatment cycles was observed. Patients received 20 mg/m^2 cisplatin and 80 mg/m^2 etoposide continuous IV infusion for three days and adriamycin 40 mg/m^2 IV the second day. Treatment courses were repeated every four weeks. Megestrol acetate, 160 mg/day, was added in six patients who had positive progesterone receptors.

Patients were evaluated for response after at least two treatment cycles, mostly three cycles. Physical examination and radiographic studies were done to quantify responses. A complete clinical response was defined as complete disappearance of all tumors for at least one month. A reduction of 50% or more in all diameters of a known disease was considered as partial response. A reduction in tumor volume which did not meet the criteria of a partial response was defined as stable disease.

All identifiable toxicities were recorded. Toxicity was graded using the criteria of the World Health Organization (WHO). Treatment was discontinued if clinical response could not be observed or significant toxicities were detected.

Results

Median age was 59 (range 41-75) and median parity of the patients was 2 (range 0-9).

Localizations of tumoral sites are demonstrated in Table 1. Twenty-three patients had received previous radiation. Two of them received radiation after the pelvic recurrence. One of the patients developed para-aortic metastasis 16 months after the primary surgery. This patient received chemotherapy after radiation. Only two of the ten para-aortic metastatic cases had bulky measurable lymph nodes before the start of the chemotherapy. Others had prior surgery and metastatic lymph nodes were resected. One of the patients with lung metastasis also had surgical resection of the metastatic tumor before chemotherapy. This patient is still alive after six years.

Thirteen cases had chemotherapy as part of their initial treatment. Chemotherapy was indicated for para-aortic metastasis in nine, peritoneal carcinomatosis in one, non-resectable pelvic tumor in one and lung metastasis in two cases.

Fifteen cases completed six courses of treatment and one had nine courses. Others had two or three cycles of treatment. Ten (38.5%) women had complete and three (11.5%) patients had partial response with an overall response rate of 50%. Median follow-up was 24 months. Surviving patients have been alive for four months and six years.

Toxicities are summarized in Table 2. Ten women had severe anemia requiring transfusion in 15 cycles. A total

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Table 1. — *Indications and sites of metastasis for chemotherapy.*

Indication	N	%
Paraaortic area	10	38.5
Lungs	5	19.2
Pelvis	9	34.6
Peritoneum	2	7.7
Total	26	100

Table 2. — *Grade 3-4 toxicities seen in patients.*

Toxicity	Patient	Cycle
Neutropenia	10	11
Febrile course	7	11
Thrombocytopenia	2	3
Anemia	10	15
GI tract bleeding	2	2

34 units of packed red blood cells was transfused. Grade 3-4 neutropenia was observed in 11 cycles of ten patients. Febrile neutropenia was seen in seven patients. Of these cases febrile episodes recurred four times. All of these patients were cured with appropriate antibiotics and suitable supportive treatments. Thrombocytopenia was observed in two women in three cycles. Five patients had short term diarrheal episodes. Two cases developed melena without obvious thrombocytopenia. Stomatitis was observed in three patients.

Treatment doses were reduced in 11 courses of seven cases. Treatment was postponed in three courses in three cases.

Discussion

The combination of cisplatin, adriamycin and etoposide in women with advanced or recurrent endometrial cancer is highly active with an objective response rate of 50% and median survival duration of 24 months in responders. Although some of the patients in this series received drugs as adjuvant treatment, the high response rate indicates it is an appropriate treatment in patients with advanced or relapsed endometrial cancer.

Lissoni *et al.* reported the results of a treatment with cisplatin, epirubicin and paclitaxel in patients with advanced, recurrent or metastatic endometrial cancer. Clinical and pathological response rates were 73% and 35%, respectively. Toxicity was significant as mainly grade 3-4 neutropenia in 61% of the patients [5]. Gebbia *et al.* reported an overall response rate of 57% with cisplatin and vinorelbine. In contrast to other combination regimens toxicity was mild [6]. Gadducci *et al.* reported an overall response rate of 43% with a combination of cisplatin, epirubicin and cyclophosphamide. However, median survival was ten months in the whole series. Median survival was 12 months in responders and nine months for the nonresponders [7]. In a study by Fung *et al.*, a 53% response rate was obtained in patients with measurable disease with a combination treatment of cisplatin, adriamycin, cyclophosphamide and medroxyprogesterone acetate [8]. All previous reports revealed a response rate of around 50% with combination chemotherapy regimens mainly including cisplatin. Toxicity was considerable and the progression-free interval and overall survival were relatively short. Sufficient prolongation in survival without significant morbidity should be essential in developing new treatment strategies.

Because endometrial cancer tends to occur in relatively older women significant toxicity is to be expected. Concomitant medical illnesses and prior radiation are the most important factors. Toxicity in this regimen was mainly hematological. Hematologic toxicity may be partially ameliorated with the use of erytropoietin and granulocyte colony stimulating factor. Gastrointestinal ulcerations and stomatitis were the most seen nonmyeloid toxicities. Delaying treatment cycles and reducing drug doses remain the main treatment modifications when significant toxicity is seen.

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