Original Articles

Filgrastim support during combination chemotherapy using cisplatin, doxorubicin, and cyclophosphamide to treat advanced or recurrent endometrial cancer: A clinical study and literature review

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Summary

In a private practice setting, 16 patients with advanced or recurrent endometrial carcinoma received cisplatinum 50 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 750 mg/m^2 every three weeks. Growth factor support using filgrastim was initiated on the first cycle of therapy and each subsequent cycle. Sixteen patients were entered into the study with 13 being evaluable. No patient had previously received chemotherapy. The overall response rate was 54% with two complete responses (15%) and five partial responses (38%). Stable disease was seen in 46% of patients. Progression-free survival was observed to be a median of 8.5 months for a complete response, a median of 8.5 months for a partial response and a median of 7 months for stable disease. Fifteen percent of the patients and 3% of all chemotherapy cycles had febrile neutropenic events. There were no deaths due to myelotoxicity. Only one patient required a dose reduction due to neutropenia. Four of the 13 patients required dose reductions due to previous nadir thrombocytopenia. Grade 4 granulocytopenia occurred in 28% of treatment cycles and grade 3 granulocytopenia occurred in 12% of treatment cycles. The use of filgrastim (G-CSF) allowed patients to stay on therapy for an average of seven treatments. Neutropenia was not the dose-limiting toxicity from this dose-intense regimen.

Kew words: Cisplatinum; Doxorubicin; Cyclophosphamide; Filgrastim; Endometrial cancer.

Introduction

Optimal treatment for advanced or recurrent endometrial carcinoma remains undefined and problematic. A variety of single agents and many combinations of chemotherapy drugs have been previously studied finding modest benefit, short duration of response, and significant toxicity [1-3]. The three-drug combination of cisplatinum, doxorubicin and cyclophosphamide is known to be active in the treatment of recurrent metastatic endometrial carcinoma and is one of the most frequently reported regimens used for this disease [6-9, 15-21]. Average overall response and complete response rates of 50% and 20% are noted in the literature [3]. Because of the toxicity of three-drug regimens, it has often been suggested that patients would be better treated with two-drug combinations such as doxorubicin and cyclophosphamide, or more recently doxorubicin with cisplatinum [2, 3]. With combination chemotherapies such as cisplatinum, doxorubicin, and cyclophosphamide (PAC), the small increase in response rate over simpler regimens has been at the expense of more frequent and more severe toxicity. It is arguable whether PAC is of clear advantage to this patient population compared to two-drug regimens.

All three chemotherapy agents in the PAC regimen have individually been confirmed to have activity in treatment of endometrial carcinoma [1]. Doxorubicin and cisplatinum are thought to have the greatest activity against recurrent endometrial carcinoma, with typical overall response rates of 20-30%. Cyclophosphamide has a lower response rate as a single agent but has frequently been combined with cisplatinum and doxorubicin since the two-drug combination of doxorubicin and cyclophosphamide may have had some increase in activity over doxorubicin alone and because the PAC regimen is commonly used in other gynecologic cancers with good response rates [3].

A literature review regarding PAC chemotherapy for treatment of endometrial carcinoma shows two reports of its use as adjuvant therapy in patients at high risk for recurrence [4, 5]. The remaining ten reports show marked differences in overall response rates, ranging from 35-75% [6-9, 15-21]. There were few complete responses obtained. Severe leukopenia of approximately 50% incidence was frequently reported [4, 6-8.]

The current study is believed to be the first trial attempting to prevent the severe myelotoxicity from PAC chemotherapy by using colony stimulating factor support of neutrophil production with filgrastim. The study was designed with the goal of avoiding disruption of the treatment schedule or the requirement for dose reduction due to myelosuppression. It was anticipated that this treatment plan would allow an optimal response rate to this combination chemotherapy while minimizing myelotoxicity from this dose-intense regimen.

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Materials and Methods

Eligibility Criteria

Following institutional review board approval of this National Biotherapy Study Group (NBSG) protocol, a total of 16 patients were entered from a private practice in this study between 1992 and 1999. Thirteen patients remain evaluable. All patients have histologically confirmed endometrial carcinoma. Study entry criteria included advanced or recurrent and metastatic endometrial cancer confirmed histologically. Patients were required to have measurable disease or to have an elevated CA-125 tumor marker greater than 100 U/ml with microscopic confirmation of disease. Twelve patients were entered with radiographically measurable disease. One patient was entered with an elevated CA-125 tumor marker. Other eligibility requirements included signed IRB approved informed consent, and an ECOG performance status of 0, 1, or 2, a serum creatinine of less than 2.0, liver function tests of serum glutamic-oxaloacetic transaminase, alkaline phosphatase, and total bilirubin of less than twice normal values. A baseline resting radionuclide ventriculography (MUGA) scan was required to confirm an ejection fraction greater than 50%. Prior to each treatment, patients were required to have had an absolute granulocyte count of greater than or equal to 1000/mm^3 and a platelet count of greater than or equal to 100,000/mm^3. Patients with prior chemotherapy were excluded from the study as were patients with significant cardiac disease. Patients were allowed to participate if they had previously received radiation therapy or hormonal therapy with a progestin. Prior to every second treatment, patients were reassessed for response.

Treatment Plan

Treatment on each cycle consisted of cisplatinum 50 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 750 mg/m^2 given intravenously and repeated every 21 days. Cisplatinum was administered in 250 cc of normal saline over 2 1/2| hours following a prior intravenous hydration and given concomitantly with diuretics of furosamide and mannitol. The doxorubicin maximum dose was limited to 75 mg on any one-treatment cycle in order to allow a prolonged use of the drug for patients who were responding to therapy. Filgrastim (G-CSF) was administered subcutaneously at a dose of 5 mcg/kg/day beginning 24 hours after chemotherapy and was continued until the post-treatment granulocyte nadir recovered to greater than or equal to 10,000/mm^3. Odansetron 0.15 mg/kg was administered intravenously prior to chemotherapy and repeated in 4-8 hours as needed for control of nausea. This was prescribed as part of the protocol in hopes of avoiding severe nausea and vomiting.

Chemotherapy was held until return of hematologic toxicity to a grade 1 level or to normal. Patients showing grade 3 or grade 4 hematologic toxicity of three days duration were to undergo a dose escalation of G-CSF to 10 mcg/kg/day. If grade 3 or grade 4 myelotoxicity recurred, then the chemotherapy dose was reduced by 25% for the next treatment cycle. A re-escalation of the dose back to 100% was to be done if the nadir absolute granulocyte count returned to grade 1 or normal. For grade 3 or grade 4 platelet toxicity (< 50,000/mm^3), a dose reduction of 25% was required. Dose escalation back to 100% of normal would occur if the nadir platelet count then remained above 50,000/mm^3 after the dose reduction. No dose reduction was empirically given to patients who had previous pelvic radiotherapy. Filgrastim was administered with the first cycle of chemotherapy. A chemotherapy dose reduction of 25% was planned for patients with grade 4 gastrointestinal toxicity. Dose escalation back to 100% would occur if no further grade 4 toxicity occurred after the dose reduction. No change in the odansetron dosage was required. Treatment was continued until progression of disease, unacceptable toxicity, or a maximum total administration of doxorubicin of 450 mgm/m^2. Patients were removed from study if the ejection fraction was less than 50% on MUGA scans or creatinine greater than 2.0, or if chemotherapy was delayed more than 60 days for any reason.

Toxicity Grading

Toxicity criteria used in this study were those of the National Biotherapy Study Group. A CBC with differential was measured twice each week during the time of filgrastim administration on each cycle and weekly measurement of basic serum chemistries, CBC, and magnesium were also obtained. A CA-125 measurement was planned for each treatment cycle. The majority of all other patients also underwent monthly assessment of serum CA-125 levels, however it was not required in every case if it was not the sole criterion for study entry and thus it was not completed in two of the 13 patients. A MUGA scan was required every three months. Definitions for grading nausea and vomiting were modified from NBSG toxicity criteria. For this study, patients with grade 1 nausea were defined as nausea occurring without vomiting; grade 2 was defined as nausea with vomiting that was controllable with oral medications; grade 3 was intractable vomiting that required IV medication and hydration but could be done successfully as an outpatient; grade 4 required hospitalization for antiemetic management or was severe vomiting occurring more than three days after chemotherapy treatment if there was no other explanation for nausea.

Criteria for Response

Patients were evaluated for response using clinical examination and chest X-ray at each treatment cycle. Assessment of the index lesion was done at least every other cycle even if a CT scan was required for measurement. Parameters for evaluation were defined according to the National Biotherapy Study Group criteria. Measurable disease was defined as any mass measurable in two diameters by examination, X-ray, CT scan, or MRI. Evaluable disease was defined as any lesion measurable by X-ray, CT scan, or MRI, but accurately measured in only one dimension or an ill-defined mass, which could not be measured in any dimension but could be appreciated with clinical assessment. CA-125 tumor marker levels had to be greater than 100 U/ml to be considered significant. Ascites was assessed as measurable disease using the severity groups of grade 3, grade 2, grade 1, or grade 0. Grade 3 was defined as examination findings of a tight abdomen due to ascites; grade 2 was an exam consistent with ascites but the abdomen was not tense or distended; grade 1 ascites was defined as no evidence of ascites on clinical exam with only CT evidence of the ascites present; grade 0 ascites was defined as neither examination or CT scan showing any evidence of ascites. A patient with a partial response of her ascites would have a decrease in severity of the grade.

A complete response was defined as the disappearance of all known disease for greater than or equal to four weeks during which time no new lesions had appeared. A partial response was the reduction of greater than or equal to 50% of the some of the products of perpendicular diameters of the index lesion. The

duration of the partial response was required to be greater than or equal to four weeks at which time no new lesions could appear. No other existing lesion separate from the index lesion could enlarge during that 4-week interval of defining a partial response. Stable disease was defined as a reduction of less than or equal to 50% or an increase of less than or equal to 50% in the sum of the products of the perpendicular diameters of all measurable lesions, and no new lesions appearing during that 4-week interval. To qualify as a stable disease there could not be any lesion (greater than 10 cm^2) at study entry that had increased by 100% from the original value. Progressive disease was defined as a greater than or equal to 100% increase in the size of any lesion or the appearance of new lesions after study entry. The duration of response was defined as the time from onset of response to subsequent progression of disease or the date of last follow-up. A progression-free interval was defined as the time from first chemotherapy until progression of disease or from the time of study entry until death if there had been no evidence of progression of disease prior to an intercurrent death. Survival was defined as the period from study entry and first treatment until the date of death or the date of last follow-up for patients lost to follow-up.

Results

A total of 16 patients were entered in the study from a private practice setting. Thirteen of these patients were evaluable for toxicity or response. Three patients originally entered in the study were deemed unevaluable because full records regarding the clinical response to treatment or toxicity could not be obtained from the treating physicians. Clinical summaries of the patients are shown in Tables 1 and 2. Ten patients had recurrent endometrial carcinoma and three patients were entered for primary treatment of their advanced cancer. Nine of the 13 patients had previously received whole pelvis external beam radiotherapy (Table 1). Five of the 13 patients had previously received progestin therapy. No patient had previously received any chemotherapy. The ECOG performance status of the evaluable patients included two at performance status 0, five at performance status 1, and six at performance status 2. Pathologic description of the original tumor from the uterine specimen identified three patients with grade 2 and ten patients with grade 3 cancers (Table 2). Histologic sub-type was endometrioid adenocarcinoma in ten, adenosquamous carcinoma in two, and clear cell carcinoma in one. Papillary serous and uterine sarcomas were not included in this study. Sites of metastatic disease included the lung in nine patients, lymph nodes in four patients including two patients with supraclavicular adenopathy and two patients with aortic adenopathy, liver metastasis in two patients, ascites in three patients, upper abdominal disease recurrence in one patient, bone metastasis involving the sacrum or hip in two patients, and a vaginal metastasis in one patient. Many patients had disease at multiple sites. No patient entered the study with recurrence limited to the pelvis or an index lesion used for evaluation in a previously irradiated field. One patient was entered with known metastasis to the aortic lymph nodes (that had been resected) and positive peritoneal cytology. She was entered in the study shortly after her primary therapeutic and staging surgery and was evaluated only by CA-125 values. Her CA-125 was 106 U/ml at the time of study entry. The indications used for termination of therapy included termination due to toxicity in five patients (39%), progressive disease in seven (54%), and a complete response to therapy in one (8%); see Table 3. One patient developed renal toxicity and was taken off therapy after her second cycle, one patient developed persistent pseudomembranous enterocolitis from Clostridium difficile and was unable to continue therapy for GI toxicity, two patients developed a measurable decrease in their cardiac ejection fraction below 50%

Table 1. — *Patient profiles: clinical variables at time of study entry.*

	No.	(%)
Disease status		
Recurrent	10	(77)
Advanced	3	(23)
Prior whole pelvic radiation		
Yes	9	(69)
No	4	(31)
Prior progestin therapy		
Yes	5	(38)
No	8	(62)
Prior chemotherapy		
Yes	0	(0)
Performance status (ECOG)		
0	2	(15)
1	5	(38)
2	6	(46)

Table 2. — *Patient profiles: histopathology and anatomy.*

	No.	(%)
Tumor grade (in uterus)		
Grade 1	–	–
Grade 2	3	(23)
Grade 3	10	(77)
Histologic subtype		
Endometrial adenocarcinoma	10	(77)
Adenosquamous	2	(15)
Clear cell	1	(8)
Papillary serous	–	(0)
Metastatic sites		
Lung	9	
Lymph nodes (non-pelvic)	4	
Suprapubic	2	
Aortic	2	
Liver	2	
Ascites	3	
Upper abdomen	1	
Bone (sacrum, hip)	2	
Vaginal	1	

*Note: Many patients had disease at multiple sites.

Table 3. — *Indication used to stop study therapy.*

	No.	(%)
Indication		
Toxicity	5	(39)
Progressive disease	7	(54)
Complete response	1	(8)

but these were both subclinical effects. No patient had measurable cardiac toxicity on conventional clinical parameters of congestive failure. One patient had a prolonged nadir thrombocytopenia and had to be taken off therapy after a partial response. The one patient who was taken off therapy after a complete response of three months duration subsequently relapsed after a disease-free interval of six months.

Two patients had a complete response, five patients had a partial response and six patients were noted to have stable disease prior to interrupting therapy due to toxicity or eventual progression. The complete response rate was 15% and the partial response rate was 38% for the entire study group. This complete plus partial response gave an overall response rate of 54% with an associated stable disease rate of 46%. Subsequent analysis of those patients who had previously undergone radiotherapy showed similar response rates when comparing the patients with prior whole pelvis radiotherapy to those who had not had previously pelvic radiotherapy.

The response to therapy was compared to the total number of doses received and the average number of doses was noted to be 6 for those with a complete response and 8.6 for those with a partial response. This information is shown in detail in Table 4. Some patients did require a decrease in dosage of chemotherapy and since this did not uniformly occur during the same treatment cycle for each patient, a comparison was made of progression-free interval vs the number of doses of chemotherapy received prior to any dose decrease. There did not appear to be any significant correlation as listed in Table 5. This is more easily understood in view of data shown in Table 5 which confirms a measurable clinical onset of response prior to administration of the second course of therapy in most of those patients with a complete or partial response.

Two patients remain alive without evidence of disease at 55 and 94 months, respectively. Neither of these patients had a complete response to chemotherapy, however one patient sustained a partial response, and after maximum doxorubicin chemotherapy underwent lung resection and has subsequently been without evidence of disease for 94 months. The other long-term survivor had a partial response for eight courses of chemotherapy and stopped therapy because of new lung lesions found after a 4-week delay of the next therapy. She then had a complete response to the other chemotherapy and after four months of treatment has remained without evidence of disease for 36 months.

The median progression-free interval for the entire study group was eight months with a similar progression-free interval regardless of the completeness of response to therapy. Table 6 shows median progression-free interval of 8.5 months for both complete response and partial response patients and six months for those with stable disease. Similar progression-free intervals were seen regardless of prior history of radiotherapy.

There were no treatment-related deaths and toxicity was felt to be modest in degree and manageable with the available support of occasional platelet transfusion and planned growth factor support using filgrastim. See Table 7 for results of the assessment of toxicity separate from myelotoxicity. Of the non-myeloid toxicities, neurotoxicity was most common but of grade 1 occurring in 21% of patients. Despite use of odansetron, grade 3 nausea and vomiting occurred in 31% of patients. Table 8 reviews myelotoxicity experienced during this study. Leukopenia was noted to be grade 4 in 30% of treatment cycles and

Table 4. — *Type of clinical response vs number of chemotherapy cycles received per patient.*

Response type	Total number of cycles received		
	Mean	Median	Range
Complete	6	6	4-8
Partial	8.6	9	8-10
Stable	5.8	5.5	2-9

No. = 13.

Table 5. — *Treatment doses received prior to dose reduction vs progression-free survival.*

Degree of response	Months PFI	Cycles prior to first response	Cycles prior to dose decrease	Dose decreased on cycle no.	Total no. cycles received
Stable	2	1	1	2	2
Stable	9	–	2	–	2
Stable	6	–	2	3	6
PR	11	1	4	5	8
CR	7	1	4	–	4
CR	10	4	5	6	8
PR	10	1	5	6	10
Stable	10	1	5	6	9
Stable	6	1	7	–	7
PR	8	2	8	–	8
PR	6	1	8	–	8
Stable	9	1	9	–	9
PR	11	2	9	–	9

Table 6. — *Progression free interval vs response type.*

Response	No.	Progression-free interval (months)		
		Median	Mean	Range
Complete	2	8.5	9	7-10
Partial	5	8.5	9	6-11
Stable disease	6	6	7	2-10
Total	13		8	

Table 7. — *Toxicity incidence (% of patients).*

Grade	1	2	3	4
Nephrotoxicity	–	(8)	–	–
Cardiotoxicity	–	–	–	–
Neurotoxicity	(21)	–	–	–
GI Mucositis	–	(8)	–	(8)
Nausea/Vomiting	(8)	(61)	(31)	–

*Note: Two patients stopped therapy because of MUGA = EF < 50% but had no clinical signs of congestive heart failure (CHF). *Note: 100% of patients alopecia.

Table 8. — *Myelotoxicity. Incidence all patients (% TX* cycles).*

Grade	1	2	3	4
Leukopenia/WBC	(2)	(7)	(26)	(30)
Granulocytopenia	(3)	(14)	(12)	(28)
Thrombocytopenia	(18)	(18)	(14)	(10)
Anemia	(27)	(27)	(4)	(0)

No. = 90 cycles. *TX = Toxicity.

Table 9. — *Myelotoxicity.*

	Prior pelvic EBRT*. Incidence (% TX** Cycles)				No pelvic EBRT. Incidence (% TX Cycles)			
Grade	1	2	3	4	1	2	3	4
Leukopenia/WBC	(1)	(7)	(26)	(35)	(4)	(9)	(26)	(4)
Granulocytopenia	(3)	(12)	(15)	(37)	(4)	(2)	(4)	(9)
Thrombocytopenia	(18)	(22)	(15)	(13)	(17)	(0)	(9)	(0)
Anemia	(24)	(28)	(6)	(0)	(36)	(27)	(0)	(0)
No. = 68 cycles.					No. = 22 cycles.			

*EBRT = External Beam Radiotherapy.
**TX = Toxicity.

grade 3 in 26% of treatment cycles. By contrast, granulocytopenia of grade 4 was 28% and grade 3 was only 12%. Thrombocytopenia of grade 4 occurred in 10% of treatment cycles and of grade 3 in 14% of treatment cycles. Table 9 shows a marked increase in severe myelotoxicity for those patients who had previously been treated with pelvic radiotherapy.

Both thrombocytopenia and neutropenia were more frequent and more severe when patients had previously been irradiated prior to chemotherapy. Thrombocytopenia of grade 3 occurred in 15% of treatment cycles and of grade 4 in 13% of treatment cycles for previously irradiated patients. By comparison, non-irradiated patients had thrombocytopenia of grade 3 in 9% and grade 4 did not occur. Platelet transfusions were administered to two of 13 (15%) patients. Platelet transfusions were administered for nadir thrombocytopenia in six of the 90 treatment cycles (7%). One patient required a platelet transfusion after courses 9 and 10 of chemotherapy. The second patient required a platelet transfusion after her fourth course of chemotherapy and again after her sixth, seventh and eighth treatments. The platelet nadir requiring transfusion was also prolonged and required a delay of the seventh and eighth chemotherapy course of two weeks for that patient. Her eighth course of treatment was for final treatment, but her platelet nadir was prolonged after that final treatment as well and after three months of treatment delays she showed a new lung nodule and was taken out of the study.

The study design included dose increase of filgrastim in an effort to prevent dose reduction of chemotherapy. If the nadir actual granulocyte count (AGC) was less than 500/mm^3 for a duration of three days or more, then the dose of filgrastim was increased to 10 mcg/kg/d for the next treatment cycle. Chemotherapy dose reduction was planned if the patient had a grade 3 or 4 nadir AGC despite the increased dose of filgrastim. Using this treatment scheme, the filgrastim dose was doubled for three patients. Those dose increases occurred after course 2 in two patients and after course 3 in one patient. There were no cycles of chemotherapy for any patient that were delayed due to slow recovery of the actual granulocyte count prior to the next scheduled dose of chemotherapy. In this study, the duration of severe granulocytopenia for patients with grade 4 toxicity was short, and recovery of AGC to greater than 1,000 occurred on average within two days. Only one of 13 patients required a chemotherapy dose reduction due to neutropenia. Two patients did develop febrile neutropenia for an incidence of 15% of patients (Table 10). Only three of 90 total treatment cycles were associated with febrile neutropenia for an incidence rate of 3% of cycles. Table 10 shows an increased rate of febrile neutropenia with previous history of pelvic radiotherapy.

Prior literature reports regarding toxicity of PAC chemotherapy for endometrial cancer patients have uniformly described myelosuppression in terms of leukopenia and total white blood cell count at nadir. To allow comparison we also calculated nadir WBC. We found grade 3 leukopenia in 28% of cycles and grade 4 leukopenia in 29% of cycles for the entire group of 13 patients. Cumulative grade 3 and grade 4 nadir leukopenia occurred in 51 of 90 (57%) cycles. When evaluating individual patients grade 4 leukopenia was noted after the first course of chemotherapy in three (23%) patients. Grade 4 leukopenia occurred sometime during multiple courses of chemotherapy in six (46%) of patients and grade 3 leukopenia in ten (77%) of patients. Grade 4 leukopenia occurred in one out of four patients with no prior history of whole pelvis radiotherapy and in six (66%) of patients who did have prior whole pelvic radiotherapy. When leukopenia severity was assessed relative to the incidence per treatment cycle, the same pattern between irradiated and non-irradiated patients was again identified. Grade 4 leukopenia occurred in 0 of 22 cycles (0%) and grade 3 in seven of 22 (32%) cycles for non-irradiated patients. Grade 4 leukopenia occurred in 26 of 68 (38%) and grade 3 in 18 of 68 (26%) for patients with prior history of whole pelvic radiotherapy.

Cumulative toxicity was apparent when evaluating the incidence of grade 3 or grade 4 thrombocytopenia at nadir relative to the number of total treatment cycles each patient had received. The trend for increased nadir toxicity was apparent for platelets, but did not change in incidence or severity for granulocytes. Table 11 shows the incidence of grade 3 and grade 4 platelet toxicity by number of cycles of chemotherapy received by each patient. Table 12 shows the granulocyte toxicity relative to the cumulative total of chemotherapy cycles received. Granulocyte toxicity seemed to be of stable severity and

Table 10. — *Incidence of febrile neutropenia.*

	No. of patients	Total patients (%)	No. of cycles	Total cycles (%)
All patients	2	13 (15)	3	90 (3)
Prior pelvic EBRT*	2	9 (22)	3	68 (4)
No pelvic EBRT*	0	4 (0)	0	22 (0)

*EBRT = External Beam Radiotherapy.

Table 11. — *Platelet toxicity vs number of cycles of chemotherapy.*

Cycle	1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)	5 No. (%)	6 No. (%)	7 No. (%)	8 No. (%)	9 No. (%)	10 No. (%)
Grade 3	0/13 (0)	1/13 (8)	0/11 (0)	1/11 (9)	4/10 (40)	1/10 (10)	1/9 (11)	3/8 (38)	1/4 (25)	0/1 (0)
Grade 4	1/13 (8)	1/13 (8)	0/11 (0)	1/11 (9)	0/10 (0)	1/10 (10)	1/9 (11)	1/8 (13)	2/4 (50)	1/1 (100)
Total (3 & 4)	1/13 (8)	2/13 (15)	0/11 (0)	2/11 (18)	4/10 (40)	2/10 (20)	2/9 (22)	4/8 (50)	3/4 (75)	1/1 (100)

No. = 13. Total patient cycles = 90.

Table 12. — *Granulocyte toxicity vs cumulative number of cycles of chemotherapy.*

Cycle	1 No. (%)	2 No. (%)	3 No. (%)	4 No. (%)	5 No. (%)	6 No. (%)	7 No. (%)	8 No. (%)	9 No. (%)	10 No. (%)	Total No. (%)
Grade 3	2/12 (17)	3/12 (25)	1/10 (10)	2/10 (20)	2/9 (22)	0/9 (0)	0/9 (0)	1/8 (13)	1/4 (25)	0/1 (0)	12/84 (14)
Grade 4	3/12 (25)	4/12 (33)	3/10 (30)	3/10 (30)	3/9 (33)	3/9 (33)	3/9 (33)	3/8 (38)	1/4 (25)	0/1 (0)	26/84 (31)
Total (3 & 4)	5/12 (42)	7/12 (58)	4/10 (40)	5/10 (50)	5/9 (55)	3/9 (33)	3/9 (33)	4/8 (50)	2/4 (50)	0/1 (0)	38/84 (45)

Total patients = 13. Total cycles = 90.

Table 13. — *Prior pac studies response and toxicity.*

Study	No. of patients	Overall responses (%)	Complete responses (%)	Partial responses (%)	Progression-free interval (mos.)	Dose reductions (%)	Neutropenia (%) grade 3/grade 4	Thrombocytopenia (%) grade 3/grade 4
Burke *et al.*, 1994	62	N/A Adjuvant	N/A	N/A	13	63	24 - 26	2 - 0
Fung *et al.*, 1991	15	53	7	47	12	75	N/A - 22	11% < 50,000
Lovecchio *et al.*, 1984	15	60	33	27	8	46	N/A - N/A	40% < 100,000
Deppe *et al.*, 1985	1	–	Had CR	–	—	N/A	Nadirs < 2,000 WBC	N/A - N/A
Turbow *et al.*, 1985	19	47	11	36	N/A	N/A	27 - 11	11% < 100,000
Hancock *et al.*, 1986	18	56	28	28	N/A	28	AGC < 1000 39%	N/A - N/A
Edmonson *et al.*, 1986	16	31	0	31	3	N/A	Median WBC Nadir < 2,000	Median Platelet Nadir < 200,000
Hoffman *et al.*, 1989	15	33	27	7	4	13	N/A - N/A	N/A - N/A
Burke *et al.*, 1991	102	45	14	31	6	50	30 - 35	4 - 0
Dunton *et al.*, 1991	25	47	17	29	10	80	N/A - 80	N/A - 12
Smith *et al.*, 1994	47	N/A Adjuvant	N/A	N/A	N/A	44	Gr 3 or Gr 4 44	N/A - N/A
Koretz *et al.*, 1980	7	57	0	57	N/A	N/A	29	N/A - N/A

frequency and this was certainly due to the study design with benefit of increasing doses of filgrastim. The trend was noted but not evaluated statistically due to the small number of patients which was aggravated by a decreasing number of patients at higher total treatment cycles. Several patients dropped out of the study after the second course and there was progressive attrition from the study due to toxicity or recurrent disease. Only one patient received ten cycles of chemotherapy.

Dose reductions during this study were done for neutropenia in one patient and for nadir thrombocytopenia on the preceding course in four patients. Dose reductions were accomplished by reducing the dosage of all three chemotherapy agents. Relative dose intensity of doxorubicin varied by body habitus because the study design required maximum doxorubicin 75 mg total dose. This was planned in an effort to ensure that patients with a good response would not have to stop treatment while enjoying a prolonged partial response. It was subsequently found that doxorubicin total dose was not the limiting factor for these patients.

CA-125 levels were assessed for most patients for most treatment cycles but no clear pattern of correlations with disease activity was seen. Only two patients entered the study treatment with a CA-125 greater than 100. One patient had stable disease with stable CA-125 as her evaluation point. The second patient had a partial response clinically while her CA-125 was rising, and that subsequently decreased several months after her exam and radiologic findings had improved. Other patients had stable or fluctuating values and no clear correlation was identified. The two patients with complete clinical response to chemotherapy were also reviewed for correlation with CA-125 levels. One patient with a complete response entered treatment with a CA-125 value of 71 and it decreased to 28 over the first four courses of chemotherapy during which time her disease had completely resolved clinically. The second patient did not have CA-125 values drawn during her first three treatment cycles and she was found to have a normal CA-125 on her fourth cycle and subsequently.

Discussion

This private practice study again confirms that the PAC regimen has activity against metastatic endometrial carcinoma for patients with recurrent or advanced cancer. Our study showed complete, partial, and overall response rates of 15%, 30%, and 54%, which are very similar to prior reports using the PAC regimen for recurrent and advanced endometrial cancer (Table 13). Stable disease that did not reach the criteria for a partial response

occurred in 46% of our patients. A comparison was made for degree of response vs the number of chemotherapy cycles received because of concern that some patients stopped therapy after only several treatments due to toxicity and would not have had equal exposure to treatment. Limited treatment might theoretically predict a lesser degree of response. Our data showed no difference in complete vs partial vs stable disease responses relative to total number of treatment cycles received (Table 4). Response rates were similar regardless of prior radiotherapy despite the pre-analysis concern that prior radiation would mean less sensitivity to chemotherapy or less tolerance to the toxic effects of the chemotherapy. The group sizes were too small to confirm significance of differences between the groups.

The time to first evidence of response was very short, averaging one month after initiation of PAC chemotherapy. Response was apparent after one cycle of therapy as measured prior to the second cycle. Three patients had persistent stable disease and therefore the time to first response was not measurable. One patient showed response after two cycles and the other nine patients showed response after the first cycle. The two patients with a complete response accomplished such by course #4 and #5, respectively. These data suggest that PAC chemotherapy can assist patients who have rapidly progressive disease who also need a prompt response for relief of symptoms. It also suggests there is little reason to wait more than three or four cycles for a response to become clinically apparent. If stable disease is seen during the first several months of therapy and if other treatment with good activity is available, it would seem reasonable to switch after a short trial of PAC instead of after cumulative toxicity has occurred.

Those patients who enjoyed a clinical response had only a modest progression-free interval that averaged eight months. This duration of response is similar to prior reports ranging from 4-13 months using the same treatment for this patient group (Table 13). Progression-free interval was not different even for patients with dose reductions done after only 2-4 cycles of therapy. Those patients who had early dose reductions were compared to those who had no dose reduction or to patients who had dose reduction on cycles 5-9. The median progression free interval was six months for those patients whose best response was stable disease, and was similar at 8.5 months for those patients with partial or complete responses. Those with stable disease of 6-10 months' duration certainly benefited from therapy. They are also an important group for analysis because they consisted of almost 50% of those patients entered in the study. The combined rate of stable disease plus partial response totaled 84% of patients entered in the study.

Thrombocytopenia was the dose limiting toxicity in our study. Grade 3 and grade 4 thrombocytopenia occurred in 24% of treatment cycles and was three times more common in patients with a history of prior radiotherapy. The effect of radiation therapy on bone marrow was apparent, in that no patient without prior radiation had a grade 4 thrombocytopenia nadir, but 13% of cycles in patients previously undergoing whole pelvis radiation did have grade 4 nadirs (Tables 8 and 9). Granulocytopenia of grade 4 occurred more frequently than did grade 4 thrombocytopenia, however, the platelet nadirs were clinically more important because of long duration. These long platelet nadirs required treatment delays for the next cycle and for one patient required the patient to drop out of the study regimen.

Thrombocytopenia was progressively worse with cumulative number of treatment cycles (Table 11). Grade 3 and 4 nadir thrombocytopenia occurred overall in 33% of cycles 4-10, but occurred in only 8% of cycles 1, 2 or 3. Thrombocytopenia of long duration and of expected repetitive nature during subsequent treatment cycles is a problem due to lack of available support. Even platelet transfusion often becomes ineffective due to sensitization to foreign antigens that shorten the duration of circulating platelet life from transfused platelets. Platelet transfusion was required in 7% of treatment cycles for this study group. By comparison, granulocyte nadirs did not become progressively worse (Table 12), and dose reduction for a low AGC nadir was rare occurring in only one of 90 cycles. Dose reduction after a low platelet nadir was required in four (38%) patients.

Dunton *et al.* [6] reported that neutropenia was the dose limiting toxicity when the PAC regimen was used for recurrent endometrial cancer. That study used a lower dose of cyclophosphamide at 500 mgm/m^2 and no G-CSF. They reported 80% of patients had grade 4 leukopenia in at least one cycle, and greater than three episodes of grade 4 leukopenia in 44% of patients. Dose reductions were used for every grade 4 nadir, and treatment was started at a 20% reduction if patients had a prior exposure to radiotherapy. Hancock *et al.* [7] treated a similar patient group, and used dose reductions for the first cycle if there was a prior history of pelvic radiotherapy and provided further dose reductions for nadir neutropenia. Their report showed five of 18 patients (28%) required dose reductions because of nadir counts. They had a 39% incidence of grade 3 plus grade 4 neutropenia. Burke *et al.* [8] treated 102 patients with recurrent or advanced endometrial cancer using PAC chemotherapy. They provided dose reductions at the outset of therapy if there was a prior history of radiotherapy. Only 40% of their patients tolerated a dose escalation after their first course of treatment. Dose reductions were made in 40% due to grade 4 nadir counts. Neutropenia occurred in 35% of patients for grade 4 toxicity and 30% of patients for grade 3 toxicity. These studies suggest a significant dose limiting myelotoxicity with the PAC regimen, particularly aggravated by prior radiotherapy. The dose reductions resulted in doses below those normally used for treatment of ovarian cancer patients, and it is possible the response rates were limited by the reduced doses.

To control for the differences in clinical variables between ovarian cancer and endometrial cancer patients, we reviewed three studies using adjuvant PAC chemotherapy after surgery without any prior radiotherapy for treat-

ment of endometrial cancer patients at high risk for recurrence [4, 5, 9]. In these three studies without prior radiotherapy, toxicity was still significant and involved a majority of patients with dose reductions due to nadir counts. Burke and co-workers [5] treated 62 endometrial cancer patients with adjuvant PAC chemotherapy prior to any radiation treatment. Dose reductions were required in 63% of these patients due to neutropenia, and 50% of patients showed grade 3 or grade 4 neutropenia. Smith *et al.* [5] used PAC chemotherapy also for postoperative adjuvant therapy in high-risk endometrial cancer patients and used it at doses of cisplatinum 50 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2. Grade 3 or grade 4 neutropenia was encountered in 44% of patients and sepsis occurred in 8% of patients. The same doses of chemotherapy were used for the PAC regimen by Stringer *et al.* [9]. That study involved 30 patients receiving PAC as postoperative operative adjuvant therapy with no preceding radiotherapy and again neutropenia grade 4 occurred in 42% and grade 3 in 27% for an overall severe neutropenia incidence of 69%.

These similarities between incidence of severe neutropenia, regardless of preceding radiotherapy, suggest that dose reductions were made prior to therapy and on an ongoing basis as needed due to preceding nadir toxicities, and therefore overall toxicity was similar since maximum tolerable doses were always administered in hopes of achieving an optimal response rate. Our study performed the same manipulations of dose with the additional support of G-CSF. We were able to use higher doses without dose reductions due to neutropenia. Dose reductions were occasionally done due to thrombocytopenia. These management decisions in all previous reports including the current one make comparisons of nadir severity and incidence uninformative without the associated information regarding doses actually administered on sequential cycles.

In the present study, patients were treated with the same dose of chemotherapy regardless of prior radiotherapy history. Starting doses of PAC were higher than those used in prior reports, as our started dose used cisplatinum 50 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 750 mg/m^2. Grade 4 neutropenia occurred in at least one cycle in 53% of patients. Febrile neutropenia occurred only in patients with prior radiotherapy and in only three of 90 cycles (3%) as shown in Table 10.

The duration of grade 4 neutropenia was short, lasting on average only four days until recovery to an AGC above 1,000/mm^3. The true duration of nadir AGC below 1,000/mm^3 was likely to have been shorter than four days, but the study design required nadir counts two times per week and the AGC was often 2,000 to 3,000/mm^3 at the time of re-measurement. Several patients did have a complete blood count two days after the first measured grade 4 nadir count, and were found to already have AGC greater than 1,000/mm^3 at that time. These short nadir durations probably prevented sepsis at the rate seen in other reports that had similar rates of neutropenia. We attribute the rapid recovery of the AGC to the use of G-CSF. The ability to use a very dose-intense regimen at what may have been 1.25 to 2.0 times the dose intensity of other studies is apparently attributable to the use of G-CSF. Our patients received a dose intensity sufficient to cause a much greater thrombocytopenia than was reported in previous studies in these previously irradiated patients with a similar degree of neutropenia. This suggests the increased dose did not have the same increase in granulocyte toxicity as it did in platelet toxicity because of the supportive effect from G-CSF.

Using this dose intense regimen did not improve the response rate for patients in this study. The lack of improved response is probably a reflection of the low activity of cyclophosphamide as a single agent, because it has a low response rate compared to single agent doxorubicin or cisplatinum. When cyclophosphamide is combined with doxorubicin it only marginally increased the response rate over doxorubicin alone [10-12]. Cisplatinum and doxorubicin together have yielded overall response rates of 45%, with 22% complete responses for recurrent endometrial cancer [13]. In that study, cisplatinum with doxorubicin had lower toxicity than has usually been reported for the PAC regimen. The above analysis suggests that the PAC regimen for endometrial carcinoma might more optimally be changed to include G-CSF and any dose reductions that would be required would reduce only the cytoxan as a first manipulation and subsequently the doxorubicin if necessary. G-CSF may be better used to decrease the toxicity of a treatment for endometrial cancer when the combination regimen has inherently greater activity than the PAC regimen. One such regimen has already been reported by Piver *et al.*, using cisplatinum, doxorubicin, and etoposide [14]. It would seem appropriate to perform phase 3 studies comparing active regimens by maintaining equal dose intensity and use G-CSF to minimize myelotoxicity so that response rates are not compromised by forced dose reduction.

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