Randomized Trial of Cisplatin Versus Cisplatin Plus Mitolactol Versus Cisplatin Plus Ifosfamide in Advanced Squamous Carcinoma of the Cervix: A Gynecologic Oncology Group Study

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Purpose: **Cisplatin, mitolactol (dibromodulcitol), and ifosfamide have been the most active single agents in squamous carcinoma of the cervix identified so far by the Gynecologic Oncology Group (GOG). Combinations of cisplatin plus ifosfamide and cisplatin plus mitolactol are prospectively compared with cisplatin alone.**

Patients and Methods: **Patients were randomized to receive cisplatin 50 mg/m^2 or the same dose of cisplatin plus mitolactol (C + M) 180 mg/m^2 orally on days 2 to 6, or cisplatin plus ifosfamide (CIFX) 5 g/m^2 given as a 24-hour infusion plus mesna 6 g/m^2 during and for 12 hours after the ifosfamide infusion, every 3 weeks for up to six courses. Of 454 patients entered, 438 were eligible and analyzed for response and survival.**

Results: **CIFX had a higher response rate (31.1% *v* 17.8%, *P* = .004) and longer progression-free survival (PFS) time (*P* = .003) compared with cisplatin alone. The median times to progression or death were 4.6 and 3.2 months, respectively. C + M showed no significant improvement in these parameters compared with cisplatin alone. Survival was associated with initial performance score (PS; 0 was more favorable; *P* < .001) and with age (younger was unfavorable, *P* = .025). There was no significant difference in overall survival between cisplatin and either of the combinations. Leukopenia, renal toxicity, peripheral neurotoxicity, and CNS toxicity were more frequent with CIFX (*P* < .05).**

Conclusion: **CIFX improved the response rate and PFS duration in advanced cervix cancer compared with cisplatin alone, but at the cost of greater toxicity and with no improvement in survival.**

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ALTHOUGH MANY PATIENTS with carcinoma of the uterine cervix are cured with local measures, a substantial minority recur or present with metastases and are potential candidates for systemic therapy. Unfortunately, the list of active drugs is short and combinations have not shown a consistent improvement over single agents.[1] Cisplatin is said to be the most active anticancer drug in cervical cancer, although 100 mg/m^2 did not significantly improve the complete response (CR) rate compared prospectively with 50 mg/m^2 (12.7 *v* 10%, respectively) and there was no appreciable difference in response duration, progression-free interval (PFI), or survival. Thus, there is no convincing reason to use a cisplatin dose higher than 50 mg/m^2.[2]

Mitolactol (dibromodulcitol) is a hexitol derivative that is converted into dianhydrogalactitol (DAG) in human serum. DAG is probably an alkylating agent. Previous studies have shown activity for both DAG[3] and mitolactol[4] in cervical cancer. A phase II study of the Gynecologic Oncology Group (GOG) demonstrated activity for mitolactol as a single agent in cervical cancer using 180 mg/m^2/d for 10 days by mouth in repeated 4-week cycles. There were 55 assessable patients, with one CR and 15 partial responses (PRs) (29% response rate).[5] The principal toxicity of mitolactol is hematologic, while that of cisplatin is nonhematologic. Since both drugs have activity in cervical cancer, it seemed reasonable to evaluate this combination.

The combination of DAG and cisplatin has previously been studied.[6] Since there were only 18 assessable patients, the study was too small for definitive conclusions. Nevertheless, the possibility existed that the combination, with two CRs and five PRs (39% response rate), produced improved results.

A pilot study used mitolactol plus cisplatin and established a tolerable dose schedule of 180 mg/m^2 of mitolactol daily for 5 days with cisplatin 50 mg/m^2.[7] Although

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an intermediate dose level (50 mg/m^2 cisplatin and 225 mg/m^2 mitolactol daily for 5 days) was considered, it was not pursued, since six of 10 patients at the first dose level in the pilot study required dose reductions and/or delays with re-treatment.

Ifosfamide is a new agent closely related to cyclophosphamide, but with less marrow toxicity and more bladder toxicity that requires concomitant use of the uroprotector mesna. Treatment of cervix cancer with the combination of ifosfamide, cisplatin, and bleomycin yielded a 69% response rate (49 patients) in one series.[8] The result was impressive, but the importance of bleomycin was unclear and its toxicity sometimes troublesome, so we proposed to compare cisplatin alone versus a regimen of cisplatin plus mitolactol (C + M) and a regimen of cisplatin plus ifosfamide (and mesna) (CIFX).

PATIENTS AND METHODS

Eligible patients included women with histologically confirmed advanced (stage IVB), recurrent, or persistent squamous cell carcinoma of the cervix not suitable for curative treatment with surgery and/or radiotherapy. Written informed consent was obtained before study entry. Lesions measurable by physical examination or chest x-ray were required. Measurements by computed tomography (CT) scan were accepted if the lesion was ≥ 3 cm and sharply defined. If a measurable lesion monitored by CT scan was less than 3 cm, it must have been confirmed by biopsy or cytology. A GOG performance score (PS) of 0, 1, or 2 (Karnofsky, 50 to 100) was required. Patients were to have recovered from effects of recent surgery or radiotherapy and be free of clinically significant infection. Originally, the protocol was less stringent about renal function and had no specification about serum albumin level. However, shortly after activation, the study was amended so that the serum creatinine concentration was to be within the institution's normal limits and the serum albumin level was to be ≥ 3 g/dL. This change was prompted by reports of encephalopathy on the ifosfamide arm (described in Results).

Ineligible patients included those with cervical neoplasms other than squamous cell carcinoma or with nonmeasurable cervical cancer, WBC count less than 4,000/μL and/or platelet count less than 100,000/μL, abnormal liver function (bilirubin, AST, or alkaline phosphatase level > two times normal not related to the cancer), bilateral hydronephrosis, GOG PS 3 or 4, past or concomitant malignancy other than skin (excluding melanoma), prior therapy with cytotoxic drugs except when used as a radiation sensitizer, radiation therapy within 3 weeks of entry, lesions measurable only by ultrasound, or pregnancy or lactation.

Patients were prospectively stratified according to whether they had received prior radiation-sensitizer treatment (hydroxyurea, cisplatin, or fluorouracil) and by PS, and were then centrally randomized with equal probability to receive (1) cisplatin 50 mg/m^2 with appropriate hydration every 3 weeks for a maximum of six courses, or (2) cisplatin 50 mg/m^2 on day 1 plus mitolactol (180 mg/m^2 orally for 5 days) on days 2 through 6 every 3 weeks, or (3) cisplatin 50 mg/m^2 plus ifosfamide 5.0 g/m^2 over 24 hours plus mesna 6 g/m^2 given concurrently with ifosfamide and for 12 hours after, every 3 weeks, again for a maximum of six courses.

The use of lorazepam was discouraged in such patients in order not to mask the possible neurotoxicity of ifosfamide. No subsequent treatment course was to begin until the WBC count was greater than 4,000/μL and the platelet count 100,000/μL. Therapy was to be delayed week by week until these levels were exceeded. Dose adjustments were specified for hematologic, gastrointestinal, renal, and neurologic toxicity. Toxicity was graded according to standard cooperative group criteria.[9] If the serum albumin level decreased to less than 3.0 g, a dose reduction of ifosfamide to 2.5 g/m^2 was specified.

CR was defined as the disappearance of all gross evidence of disease for at least 4 weeks. PR was a ≥ 50% reduction in the product obtained from the measurement of each lesion for at least 4 weeks.

Statistical Considerations

The design for this study was based on the assumption that a 15% increase in the response rate due to the addition of either mitolactol or ifosfamide to cisplatin would be regarded as clinically meaningful. Therefore, the primary objective of this study was to compare the proportion of patients who responded to the cisplatin-only regimen versus each of the combination regimens. The null hypothesis was rejected if the probability of the observed result, or a more extreme result, under the null hypothesis was less than 0.025 (one-tail test). A linear logistic model was used to adjust for age, PS, and whether cisplatin had been used as a radiosensitizer.[10] The adjusted relative risk of survival and progression-free survival (PFS) was assessed with a linear proportional hazards model.[11]

Ten patients did not receive the randomized study treatment. These women are classified as nonresponders and grouped by randomized treatment in an intent-to-treat analysis. They are also included in the analysis of overall survival and PFS, but are not included in the summary of toxicity. Toxicities are compared between treatment groups by a Kruskal-Wallis rank test (two-tail), adjusting for ties.[12]

RESULTS

Between June 1990 and January 1994, 454 women entered the study of whom 16 were ineligible (wrong stage, n = 2; wrong cell type, n = 9; wrong primary tumor, n = 2; prior chemotherapy, n = 2; second primary tumor, n = 1), which left 438 eligible patients (including 10 who received no drug; all were included in the intent-to-treat analysis). Thus, there were 140 eligible patients on the cisplatin arm, 147 on the C + M arm, and 151 on the CIFX arm. Patient pretreatment characteristics were well balanced among the three arms (Table 1).

Toxicity

There was more granulocytopenia, thrombocytopenia, and leukocytopenia associated with C + M compared with cisplatin alone ($P < .025$). Also, more granulocytopenia, thrombocytopenia, and nausea and vomiting were associated with CIFX versus cisplatin alone ($P < .025$) (Table 2). One patient died of urosepsis after six courses of C + M at a time when her blood counts were moderately depressed. One patient developed renal failure after one course of CIFX and died after she had refused dial-

Table 1. Patient Characteristics

Characteristic	Regimen					
	Cisplatin (n = 140)		C+M (n = 147)		CIFX (n = 151)	
	No	%	No.	%	No.	%
Age, years						
Median	47.3		48.8		46.3	
Range	24-85		22-84		23-83	
GOG PS						
0	59	42.1	57	38.8	67	44.4
1	61	43 6	70	47.6	62	41.1
2	20	14.3	20	13.6	22	14 6
Prior radiotherapy	123	87 9	127	86.4	128	84.8
Prior radiosensitizer						
Hydroxyurea	17	12 1	21	14.3	17	11 3
Cisplatin ± fluorouracil	19	13.6	24	16.3	21	13 9
Histologic grade*						
1	8	5.7	10	6.8	1	1.0
2	80	57.1	76	51.7	86	57 5
3	52	37.1	61	41.5	63	42.0
Site of disease						
Pelvic	68	48.6	60	40 8	74	49.0
Extrapelvic	63	45.0	70	47.6	62	41.1
Both	9	6.4	17	11.6	15	9.9
No. of courses						
Median	4		3		4	
Range	0-8		0-7		0-8	
No. not treated	3		2		5	

*One not specified.

ysis. Peripheral (P = .013) and central neurotoxicity (P = .001) were both significantly more frequent and severe with CIFX compared with cisplatin alone (Table 3), but not so for C + M. CNS toxicity ranged from confusion to somnolence to coma and/or seizures. In some patients, fatigue or weakness was reported and ascribed to chemotherapy. In all cases except one fatal case, CNS toxicity was reversible. In that case, which occurred early in the trial, the patient had a cardiorespiratory arrest while comatose. As a result, the eligibility criteria for the trial were revised. Subsequent patients were required to have a pretreatment serum albumin level ≥ 3.0 g/dL and a serum creatinine concentration within the institution's normal limits, and patients with bilateral hydronephrosis were ineligible. These changes were based on a previous report that suggested low serum albumin level, high creatinine concentration, and the presence of pelvic tumor were correlated with severe encephalopathy.[13] Subsequently, no fatal CNS toxicity was observed, but lesser degrees of encephalopathy continued to be observed more frequently on the CIFX arm.

Response and Survival

There was a significantly greater frequency of response (31.1%) among patients treated with CIFX compared with cisplatin alone (17.8%; P = .004; Table 4). The frequency of response among those treated with C + M (21.1%) was only slightly greater than cisplatin and not statistically significant. The median durations of response among those who did respond were 5.5, 7.7, and 10 months,

Table 2. Toxicity

Drug Regimen	Toxicity Grade																			
	Granulocytes					Platelets					Nausea-Vomiting					Creatinine				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Cisplatin (n = 137)	126	6	4	1	0	129	7	0	1	0	83	22	20	9	3	128	4	3	1	1
C+M (n = 145)	104	8	14	16	3	65	40	17	12	11	83	22	30	7	3	139	2	4	0	0
CIFX (n = 146)	81	5	5	16	39	77	24	17	14	14	65	20	44	12	5	129	2	5	6	4*

*One fatality; patient refused dialysis.

Table 3. Neurotoxicity

Drug Regimen	Grade: Peripheral 0	1	2	3	4	Central 0	1	2	3	4	Total
Cisplatin*	134	3	0	0	0	133	2	1	1	0	137
C+M	140	2	0	3	0	141	1	2	1	0	145
CIFX	133	7	4	2	0	105	5	10	19	7†	146

*More severe peripheral ($P = .013$) and central ($P < .0001$) toxicity with CIFX than with cisplatin alone.

†One fatality; pretreatment serum albumin level, 2.4 g/dL; protocol subsequently revised to require albumin of at least 3.0 g/dL.

respectively, for cisplatin alone, C + M, and CIFX. There were 34 stage IVB patients, of whom 31 had no prior radiotherapy; seven of 31 (23%) had a response to protocol chemotherapy. Response by site of measurable disease is listed in Table 5.

PFS (Fig 1) adjusted for age, PS, and prior cisplatin as a radiosensitizer was statistically significantly longer for CIFX (median, 4.6 *v* 3.2 months) compared with cisplatin alone ($P = .003$); however, there was no difference between C + M and cisplatin alone.

There was no significant difference in survival between cisplatin and either of the combination regimens (median [months]: cisplatin, 8.0; C + M, 7.3; CIFX, 8.3; $P = .835$) (Fig 2). Age was associated with survival ($P = .025$), with younger age being unfavorable (Fig 3); this, in turn, was correlated with a shorter time from diagnosis to study entry. Initial PS (not shown) was also associated with survival (PS 0 was favorable; $P < .001$); the median durations of survival for PS 0, 1, and 2 were 10.0, 7.4, and 6.8 months, respectively. Histologic grade and prior radiotherapy were not significantly associated with survival.

Chemotherapy concurrently with definitive radiation therapy as a radiosensitizer has been used in some cases of cervix cancer in recent years. As a consequence, a subset of patients in the present study had such a prior history (Table 1). The treatment arms were well balanced in this regard and there was no evidence that the treatment comparisons were distorted by this prior treatment. Nevertheless, among those who received cisplatin as a radiosensitizer, the risk of death was 47% greater than for those who received prior irradiation without a radiosensitizer ($P < .01$).

DISCUSSION

The results of this trial in cervix cancer reflect a common set of findings in combination chemotherapy of advanced solid tumors, namely, a higher response rate (but not a high CR rate) with a combination compared with single-agent therapy at the cost of more toxicity and no survival benefit. In the present trial, there was a significant improvement in PFS associated with CIFX; however, its impact on the patient's sense of well-being was not assessed. Since there was no overall survival improvement, it is unclear to what extent the improvement in PFS or in response rate actually benefitted the patients.

A phase II trial of bleomycin plus ifosfamide plus cisplatin that used the same dose schedules of CIFX as in the present trial achieved a 20% CR rate.[8] In that study, the patients tended to be younger, but no criteria for lung function were given and no pulmonary toxicity was reported. Since the role of bleomycin in cervix cancer is unclear, but implies restricting therapy to patients with good pulmonary function, we elected not to include bleomycin in the present study. Early experience in randomized phase II trials suggested that bleomycin and vincristine contributed importantly to combination regimens,[14,15] but other randomized phase II trials have not supported a major role for these agents.[16-18] It remains to be seen whether the addition of bleomycin will be helpful; that is the subject of a current randomized trial.

Table 4. Response Rates

Response	Cisplatin No	%	C+M No	%	CIFX No	%	Total
CR	9	6.4	14	9.5	19	12.6	42
PR	16	11.4	17	11.6	28	18.5	61
No response	115	82.1	116	78.9	104	68.9	335
Total	140	100.0	147	100.5	151	100.0	438

NOTE. Denominators include 3, 2, and 5 patients, respectively, who were not treated

Table 5. Site of Measurable Disease Versus Response

Response	Site of Measurable Disease: Pelvic No	%	Extrapelvic No	%	Combination No	%	Total
CR	20	9.9	21	10.0	1	2.4	42
PR	17	8.4	40	20.5	4	9.8	61
No response	165	81.7	134	68.7	36	87.8	335
Total	202		195		41		438

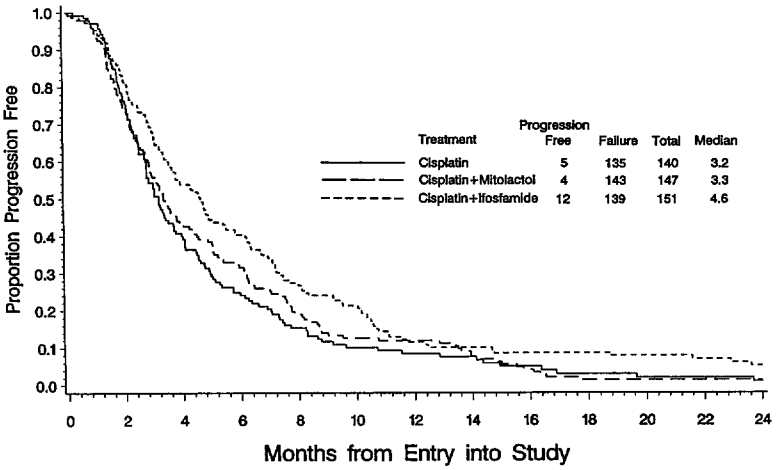

Fig 1. Proportion surviving progression-free by treatment group.

The C + M regimen was well tolerated, but disappointing. Mitolactol is clearly active in advanced cervix cancer as a single agent using a schedule of 180 mg/^{2}/d for 10 days every 4 weeks.[5] The pilot study on which the C + M arm of the present trial was based identified 180 mg/m^2 for 5 days as the maximum-tolerated dose in combination with cisplatin. Perhaps that dose of mitolactol is too low to provide an additional effect with cisplatin.

A report that indicated mitolactol therapy of breast cancer was associated with myelodysplasia and secondary leukemias[19] is of concern. Although we are not aware of such complications in the present trial, the possible risk of secondary malignancies plus the failure to show an improvement in outcome for C + M would suggest a limited future for mitolactol in the treatment of cervix cancer.

There is a paucity of phase III chemotherapy trials in advanced cervix cancer. It appears that studies are limited to a comparison of doxorubicin with or without vincristine and doxorubicin plus cyclophosphamide[20] (n = 174), with no difference in response rate, PFI, or survival; a comparison of cisplatin dose schedules, already referred to[2]; a study of cisplatin infusion time[21] (N = 331); and a comparison of carboplatin versus iproplatin[22] (N = 361), with no difference in response rate, PFI, or survival. A survival benefit was reported in a small trial (25 patients) in favor of cisplatin plus methotrexate over hydroxyurea, but prerandomization was used, PS was not accounted for, and there may have been other imbalances in the treatment arms that could account for the difference in outcome.[23] The methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) regimen, popularized in the treatment of transitional cell bladder cancer, has recently been reported to be active in cervix cancer.[24,25] A large randomized trial will be required to put that regimen in perspective. Clearly, a select patient population without

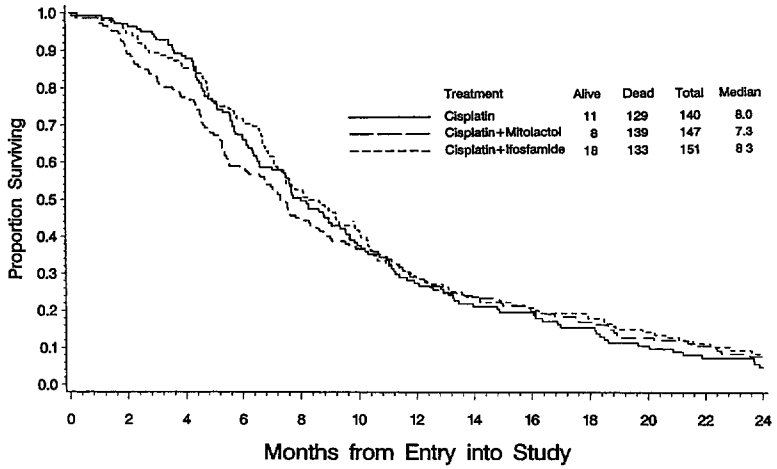

Fig 2. Survival by treatment group.

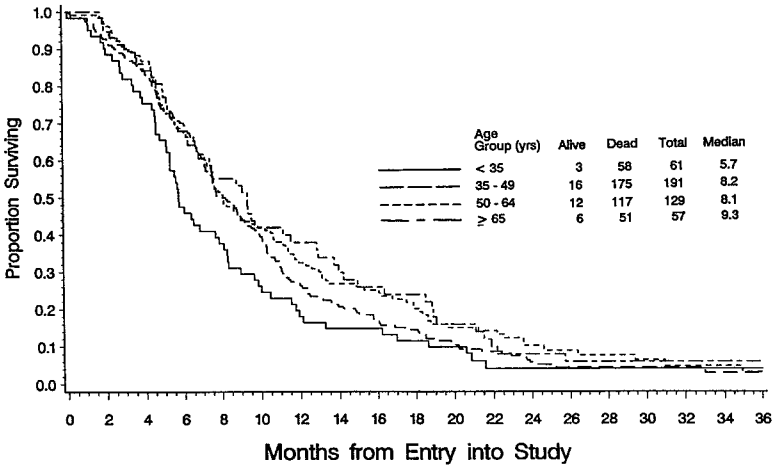

Fig 3. Survival by age group.

obstructive uropathy, and without renal or cardiac disease, is preferred for such a regimen.

Cisplatin alone has limited value in advanced cervix cancer; we are not aware of a randomized trial of cisplatin versus supportive care. Such a study would be of great interest. One of the earlier GOG trials[2] showed an improved overall response rate (31.4% *v* 20.7%; $P = .015$) with double-dose cisplatin (100 mg/m^2), but no improvement in CR rate, PFI, or survival. In contrast, the present trial, which used cisplatin 50 mg/m^2 plus ifosfamide, has shown an impact on PFS. Perhaps this is a step in the right direction, albeit with more toxicity. In fact, this appears to be the first evidence of an impact of a chemotherapy regimen on PFS in advanced cervix cancer. Whether this can be translated into a survival benefit by the addition of bleomycin remains to be determined. More likely, a new generation of highly active agents will be required to move forward. Fortunately, curative local therapy is available when this disease is diagnosed at a much earlier stage.

APPENDIX

The following GOG institutions participated in this study: University of Alabama at Birmingham, Oregon Health Sciences Center, Duke University Medical Center, Temple University Health Science Center Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University School of Medicine, University of Minnesota Medical School, University of Southern California Medical Center at Los Angeles, University of Mississippi Medical Center, Colorado Foundation for Medical Care, University of California Medical Center at Los Angeles, University of Washington Medical Center, Hospital of the University of Pennsylvania, University of Miami School of Medicine, The Milton S. Hershey School of Medicine of the Pennsylvania State University, Georgetown University Hospital, University of Cincinnati College of Medicine, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Health Science Center at Dallas, Indiana University Medical Center, Bowman Gray School of Medicine of Wake Forest University, University of California Medical Center at Irvine, Tufts New England Medical Center, Illinois Cancer Council, Stanford University Medical Center, State University of New York Downstate Medical Center, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, The Johns Hopkins Oncology Center, State University of New York at Stony Brook, Pennsylvania Hospital, Washington University School of Medicine, Cooper Hospital University Medical Center, Columbus Cancer Council, University of Texas M.D. Anderson Cancer Center, University of Massachusetts Medical Center, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center of Northern California, University of Oklahoma, University of Chicago, and Tacoma General Hospital.

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