CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

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ABSTRACT

Background and Methods On behalf of the Gynecologic Oncology Group, we performed a randomized trial of radiotherapy in combination with three concurrent chemotherapy regimens — cisplatin alone; cisplatin, fluorouracil, and hydroxyurea; and hydroxyurea alone — in patients with locally advanced cervical cancer. Women with primary untreated invasive squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix of stage IIB, III, or IVA, without involvement of the para-aortic lymph nodes, were enrolled. The patients had to have a leukocyte count of at least 3000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a serum creatinine level no higher than 2 mg per deciliter (177 μmol per liter), and adequate hepatic function. All patients received external-beam radiotherapy according to a strict protocol. Patients were randomly assigned to receive one of three chemotherapy regimens: 40 mg of cisplatin per square meter of body-surface area per week for six weeks (group 1); 50 mg of cisplatin per square meter on days 1 and 29, followed by 4 g of fluorouracil per square meter given as a 96-hour infusion on days 1 and 29, and 2 g of oral hydroxyurea per square meter twice weekly for six weeks (group 2); or 3 g of oral hydroxyurea per square meter twice weekly for six weeks (group 3).

Results The analysis included 526 women. The median duration of follow-up was 35 months. Both groups that received cisplatin had a higher rate of progression-free survival than the group that received hydroxyurea alone (P<0.001 for both comparisons). The relative risks of progression of disease or death were 0.57 (95 percent confidence interval, 0.42 to 0.78) in group 1 and 0.55 (95 percent confidence interval, 0.40 to 0.75) in group 2, as compared with group 3. The overall survival rate was significantly higher in groups 1 and 2 than in group 3, with relative risks of death of 0.61 (95 percent confidence interval, 0.44 to 0.85) and 0.58 (95 percent confidence interval, 0.41 to 0.81), respectively.

Conclusions Regimens of radiotherapy and chemotherapy that contain cisplatin improve the rates of survival and progression-free survival among women with locally advanced cervical cancer. (N Engl J Med 1999;340:1144-53.)

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CERVICAL cancer is the second most frequent cancer among women worldwide and the most frequent cancer among women in Africa, Asia, and South America.[1] In the United States, where screening for cervical cancer is readily available, most women who are found to have cervical cancer were not screened regularly.[2] As a result, about 25 percent of patients with cervical cancer in the United States present with locally advanced disease (stage IIB through IVA according to the staging system of the International Federation of Gynecology and Obstetrics).[3,4]

The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue.[5] Efforts to overcome this problem have included the use of large-particle radiotherapy, the use of different radiation-fractionation schedules, and the concurrent use of hyperthermia or chemotherapy.

Theoretically, chemotherapy and radiotherapy could have a synergistic effect; for example, the chemotherapy might increase the sensitivity of the tumor to radiation. Moreover, radiotherapy could be used for local disease while chemotherapy is used for systemic disease.[6] Concurrent chemotherapy inhibits the repair of sublethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle, and is cytotoxic in vitro.[7-9] The concurrent use of single-drug and multiple-drug regimens with radiotherapy has been tested in women with cervical cancer, but combination therapy has not gained wide acceptance.[10]

The Gynecologic Oncology Group has performed several prospective, randomized studies of the effect of concurrent chemotherapy and radiotherapy in women with locally advanced cervical cancer. Radio-

therapy combined with treatment with hydroxyurea has been compared in separate trials with radiotherapy alone, with radiotherapy and concomitant therapy with misonidazole, and with radiotherapy and concomitant treatment with cisplatin and fluorouracil[11-13] (and Whitney CW: unpublished data). As compared with radiotherapy alone, treatment with hydroxyurea and radiotherapy significantly increased the rate of complete response, progression-free survival, and overall survival.[11] As compared with treatment with misonidazole and radiotherapy, treatment with hydroxyurea and radiotherapy increased progression-free survival and was less toxic.[12,13] However, treatment with cisplatin, fluorouracil, and radiotherapy resulted in greater improvement in progression-free survival and overall survival than did treatment with hydroxyurea and radiotherapy (Whitney CW: unpublished data).

At the time we were developing the protocol used in the current study, radiotherapy plus concomitant chemotherapy with hydroxyurea was the standard combined-therapy regimen for advanced cervical cancer, because an early analysis of the combination of radiation, cisplatin, and fluorouracil failed to show improved progression-free survival. However, myelosuppression is a limiting toxic effect of treatment with hydroxyurea, whereas cisplatin is less myelosuppressive and can be given weekly during radiotherapy, with acceptable levels of toxicity.[14-17] In our study, to improve the efficacy of the cisplatin and fluorouracil combination, we added hydroxyurea to the regimen, because of evidence that this drug inhibits ribonucleotide reductase and depletes tumor cells of deoxyuridine monophosphate.[18] The depletion of deoxyuridine monophosphate may be important because this compound competes with the active metabolite of fluorouracil, fluorodeoxyuridine monophosphate, for the binding of thymidylate synthase. In addition, the responses in phase 2 trials of this chemotherapy regimen with radiotherapy in patients with cervical cancer and in patients with head and neck cancer were favorable.[19,20] Therefore, we undertook a randomized study in which all women with locally advanced cervical cancer received local radiation as well as weekly concomitant treatment with cisplatin alone; the combination of cisplatin, fluorouracil, and hydroxyurea; or hydroxyurea alone.

METHODS

Eligibility

The institutions that participated in the study are listed in the Appendix. Women with untreated invasive squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix of International Federation of Gynecology and Obstetrics stage IIB (localized disease with parametrial involvement), stage III (extension of the tumor to the pelvic wall), or stage IVB (involvement of the bladder or rectal mucosa) were enrolled in the study from April 1992 to April 1997. All cancers were confirmed histologically by the Gynecologic Oncology Group pathology committee. Patients

with disease outside the pelvis and those with metastasis to para-aortic lymph nodes or intraperitoneal disease were not eligible.

Each patient was required to undergo a complete physical examination, a pelvic examination under anesthesia, chest radiography, and intravenous pyelography or abdominal computed tomography to determine the clinical stage of the cancer. In addition, patients were required to have undergone a specific type of extraperitoneal para-aortic lymphadenectomy.[21] Patients were required to have a Gynecologic Oncology Group performance status of 0, 1, 2, or 3 (equivalent to Karnofsky performance scores of 90 or 100, 70 or 80, 50 or 60, and 30 or 40, respectively) and to have no history of other cancers.

Other eligibility criteria were as follows: a leukocyte count of at least 3000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a serum creatinine level of no more than 2.0 mg per deciliter (177 μmol per liter), a serum bilirubin level that was no more than 1.5 times the upper limit of normal at the institution where it was measured, and a serum aspartate aminotransferase level that was no more than 3 times the upper limit of normal at the institution where it was measured. Additional pretreatment evaluations included assessment of performance status and measurements of the cervical tumor and serum electrolytes and magnesium. All patients gave written informed consent according to institutional, state, and federal regulations.

Radiotherapy

Radiotherapy was administered to the whole pelvic region in 24 fractions totaling 40.8 Gy or 30 fractions totaling 51.0 Gy, followed one to three weeks later by intracavitary brachytherapy (the insertion of a radioactive implant). Either one or two intracavitary implants were inserted. The total dose delivered was 40 Gy in patients with stage IIB and 30 Gy in patients with stage III or IVA disease. The total dose delivered to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 80.8 Gy in patients with stage IIB and 81.0 Gy in patients with stage III or IVA disease; the total dose delivered to point B (the pelvic wall) was 55.0 Gy in patients with stage IIB disease and 60.0 Gy in patients with stage III or IVA disease. Pelvic radiation was delivered by anteroposterior and posteroanterior parallel ports or a four-field box technique (anteroposterior, posteroanterior, and two lateral fields) with an x-ray energy of at least 4-MV photons. The pelvic field extended from the upper margin of L5 to the midportion of the obturator foramen or the lowest level of disease, with a 3-cm margin, and laterally 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall (at least 7 cm from the midline). For the lateral fields, the anterior border was the anterior border of the pubic symphysis and the posterior border was the space between S2 and S3. The fields could be modified to include areas of known tumor.

If two intracavitary applications were used, the second was to be given within two weeks after the first implant. If intracavitary brachytherapy could not be delivered, the tumor was treated with additional external-beam radiotherapy, for a total dose of 61.2 Gy. Interstitial and high-dose brachytherapy were not allowed.

The duration of the radiotherapy was 10 weeks. Radiotherapy was withheld if a patient had a leukocyte count of less than 2000 per cubic millimeter, and delays of up to one week were also allowed in the event of radiation-related gastrointestinal or genitourinary toxicity. The length of delays in radiotherapy, in days, was calculated by subtracting the planned duration of radiotherapy (the number of prescribed fractions plus 2 weekend days for every five fractions plus 10 days for each implant) from the actual duration of radiotherapy. The Radiological Physics Center in Houston reviewed all technical aspects of radiotherapy and verified the calibration of the instruments used.

Chemotherapy

The patients were randomly assigned to receive one of three chemotherapy regimens, which were given concomitantly with external-beam radiotherapy (Table 1). Treatment with hydroxy-

TABLE 1. CHEMOTHERAPY SCHEDULES AND DOSE MODIFICATIONS.

VARIABLE	DOSE*			DOSE MODIFICATION
	CISPLATIN	FLUOROURACIL	HYDROXYUREA	
Regimen				
Cisplatin	40 mg/m² of body-surface area IV 4 hr before radiotherapy at weeks 1–6			
Cisplatin, fluorouracil, and hydroxyurea	50 mg/m² IV on days 1 and 29	4 g/m², as a 96-hour infusion, on days 1 and 29	2 g/m² orally twice weekly 2 hr before radiotherapy at weeks 1–6	
Hydroxyurea			3 g/m² orally twice weekly 2 hr before radiotherapy at weeks 1–6	
Adverse effect†				
Leukopenia				
Grade 3				Fluorouracil, 750 mg/m²
Grade 4				Fluorouracil, 500 mg/m²
Thrombocytopenia				
Grade 3				Fluorouracil, 750 mg/m²
Grade 4				Fluorouracil, 500 mg/m²
Stomatitis or diarrhea				
Grade 3				Fluorouracil, 750 mg/m²
Grade 4				Fluorouracil, 500 mg/m²
Neurotoxicity				
Grade 2				Cisplatin, 30 mg/m²
Grade ⩾3				Cisplatin discontinued
Emesis				
Grade 4				Cisplatin, 30 mg/m²
Renal abnormalities (serum creatinine, ⩾2.0 mg/dl)				Cisplatin discontinued

*IV denotes intravenously.

†Adverse effects were assessed with use of the National Cancer Institute Common Toxicity Criteria. A grade of 3 indicates a moderate effect, and a grade of 4 a severe effect.

urea or fluorouracil was discontinued if the leukocyte count dropped below 3000 per cubic millimeter or the platelet count dropped below 100,000 per cubic millimeter, and it was resumed once the counts rose above these levels. Treatment with cisplatin was discontinued if the leukocyte count dropped below 2500 per cubic millimeter or the platelet count dropped below 50,000 per cubic millimeter, and it was resumed once the counts rose above these levels. Adverse effects that required modifications in the doses in subsequent cycles are shown in Table 1.

Statistical Analysis

The primary end points were survival and progression-free survival. Progression was defined as a 50 percent increase in the product of the two largest diameters of the primary tumor or metastasis. Progression-free survival was calculated from the date of entry into the study to the date of the first physical or radiographic evidence of disease progression, death, or the last follow-up visit. Survival was calculated from the date of entry into the study to the date of death or the last follow-up visit.

We calculated the target sample size of 165 patients for each regimen on the basis of an ability to detect a 35 percent decrease in the rate of disease progression with the use of either radiotherapy combined with treatment with cisplatin or radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea. The design called for final analysis when disease progression (or death) had occurred in 104 patients receiving the control regimen (radiotherapy combined with treatment with hydroxyurea). This design provided the study with a statistical power of 80 percent with the use of the log-rank test at an alpha level of 0.025 (by one-tailed test).[22] At the time of this analysis 104 patients had had progression of disease in the control group and 89 patients had died, with or without disease progression — 86 percent of

the number of deaths needed for a final analysis of survival. Thus, because of the large difference in outcome among the treatment groups and the similarity between the rates of survival and progression-free survival within each of the treatment groups, this analysis is the final analysis of survival and progression-free survival.

Randomization was carried out by a block arrangement; the treatment assignments were stratified according to center and the three clinical stages of disease, with approximately equal numbers assigned to each treatment group. Life-table estimates were calculated according to the method of Kaplan and Meier,[23] and differences in progression-free survival were evaluated with use of the log-rank test according to the intention-to-treat principle.[24] The Cox model was used to adjust for prognostic factors and to estimate the relative likelihood (and 95 percent confidence intervals) of survival and progression-free survival.[25] Pearson's chi-square test was used to detect differences in the incidence of adverse effects among treatment regimens.[26] All reported P values are two-tailed unless otherwise stated.

Interim analyses were conducted in May 1994, November 1995, and November 1996 with the use of prespecified critical values (11.1, 10.6, and 10.6, respectively) for the log-rank test with two degrees of freedom. The performance of these interim tests raised the type I error by only 0.05 percent. Because of this negligible increase and to simplify the presentation, the P values were not adjusted for the results of the interim analyses.

RESULTS

Characteristics of the Patients

From April 1992 to April 1997, 575 patients were enrolled: 192 were assigned to receive radiotherapy

TABLE 2. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	RADIOTHERAPY AND CISPLATIN (N=176)	RADIOTHERAPY AND CISPLATIN, FLUOROURACIL, AND HYDROXYUREA (N=173)	RADIOTHERAPY AND HYDROXYUREA (N=177)
	no. of patients (%)		
Histologic diagnosis			
Adenocarcinoma	5 (2.8)	8 (4.6)	5 (2.8)
Adenosquamous carcinoma	13 (7.4)	11 (6.4)	6 (3.4)
Squamous-cell carcinoma	157 (89.2)	152 (87.9)	163 (92.1)
Other	1 (0.6)	2 (1.2)	3 (1.7)
Tumor grade†			
1	15 (8.5)	10 (5.8)	13 (7.3)
2	116 (65.9)	106 (61.3)	128 (72.3)
3	45 (25.6)	56 (32.4)	34 (19.2)
Unknown	0	1 (0.6)	2 (1.1)
Age (yr)			
≤30	7 (4.0)	10 (5.8)	9 (5.1)
31–40	49 (27.8)	42 (24.3)	38 (21.5)
41–50	50 (28.4)	45 (26.0)	53 (29.9)
51–60	34 (19.3)	44 (25.4)	51 (28.8)
61–70	32 (18.2)	24 (13.9)	21 (11.9)
≥71	4 (2.3)	8 (4.6)	5 (2.8)
Race or ethnic group			
White	101 (57.4)	97 (56.1)	105 (59.3)
Black	45 (25.6)	40 (23.1)	45 (25.4)
Hispanic	24 (13.6)	23 (13.3)	20 (11.3)
Asian	5 (2.8)	10 (5.8)	5 (2.8)
Other	1 (0.6)	3 (1.7)	2 (1.1)
Karnofsky performance score			
90 or 100	104 (59.1)	89 (51.4)	88 (49.7)
70 or 80	63 (35.8)	73 (42.2)	70 (39.5)
50 or 60	9 (5.1)	10 (5.8)	17 (9.6)
30 or 40	0	1 (0.6)	2 (1.1)
FIGO stage‡			
IIB	101 (57.4)	80 (46.2)	94 (53.1)
IIIA	3 (1.7)	7 (4.0)	5 (2.8)
IIIB	68 (38.6)	80 (46.2)	72 (40.7)
IVA	4 (2.3)	6 (3.5)	6 (3.4)
Tumor size (cm)§			
≤4.0	25 (14.2)	30 (17.3)	21 (11.9)
4.1–5.0	21 (11.9)	18 (10.4)	33 (18.6)
5.1–6.0	47 (26.7)	46 (26.6)	49 (27.7)
6.1–7.0	27 (15.3)	29 (16.8)	24 (13.6)
7.1–8.0	30 (17.0)	30 (17.3)	24 (13.6)
≥8.1	23 (13.1)	18 (10.4)	21 (11.9)
Unknown	3 (1.7)	2 (1.2)	5 (2.8)
Parametrial involvement			
No	0	3 (1.7)	2 (1.1)
Unilateral	86 (48.9)	84 (48.6)	84 (47.5)
Bilateral	89 (50.6)	80 (46.2)	85 (48.0)
Unknown	1 (0.6)	6 (3.5)	6 (3.4)
Pelvic-node status			
Positive	22 (12.5)	21 (12.1)	29 (16.4)
Negative	70 (39.8)	68 (39.3)	64 (36.2)
Not assessed	84 (47.7)	84 (48.6)	83 (46.9)
Unknown	0	0	1 (0.6)

*Because of rounding, not all percentages total 100.

†A grade of 1 indicates that 75 percent of cells were well differentiated, a grade of 2 that 50 percent of cells were well differentiated, and a grade of 3 that less than 25 percent of cells were well differentiated.

‡FIGO denotes International Federation of Gynecology and Obstetrics.

§The tumor size was determined by physical examination.

and concomitant chemotherapy with cisplatin; 191 were assigned to receive radiotherapy and concomitant chemotherapy with cisplatin, fluorouracil, and hydroxyurea; and 192 were assigned to receive radiotherapy and concomitant chemotherapy with hydroxyurea. Forty-nine of these patients (9 percent) were subsequently found to be ineligible for the following reasons: because of deviations from the surgical protocol for the evaluation of para-aortic lymph nodes (44 patients), ineligible stage of disease (2), metastasis to para-aortic lymph nodes (1), incorrect primary diagnosis (1), and incomplete pretreatment testing (1). Thus, a total of 526 patients were included in the analysis: 176 in the group given radiotherapy combined with cisplatin therapy; 173 in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 177 in the group given radiotherapy combined with hydroxyurea therapy.

There were no significant differences in the clinical characteristics among the three treatment groups (Table 2). The analyses reported here were performed in December 1998.

Progression-free Survival

The relative risk of progression of disease or death was 0.57 (95 percent confidence interval, 0.42 to 0.78) in the group given radiotherapy combined with cisplatin therapy and 0.55 (95 percent confidence interval, 0.40 to 0.75) in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea, as compared with the group given radiotherapy combined with hydroxyurea therapy, after adjustment for the clinical stage of disease. Patients who received the platinum-based regimens had significantly longer progression-free survival than those who received hydroxyurea (P<0.001 for both comparisons) (Fig. 1). A multiple regression analysis of progression-free survival was performed that included the prognostic variables identified by Stehman et al.[27]: clinical stage of disease, tumor size as assessed by physical examination, status of pelvic lymph nodes, age at diagnosis, and performance status. After adjustment for these five factors, the relative risks of disease progression for the group given radiotherapy combined with cisplatin therapy and the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea were extremely close (relative risks, 0.58 and 0.55, respectively) to the estimates obtained after adjustment for clinical stage of disease alone. The rates of progression-free survival at 24 months were 67 percent in the group given radiotherapy combined with cisplatin therapy; 64 percent in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 47 percent in the group given radiotherapy combined with hydroxyurea therapy.
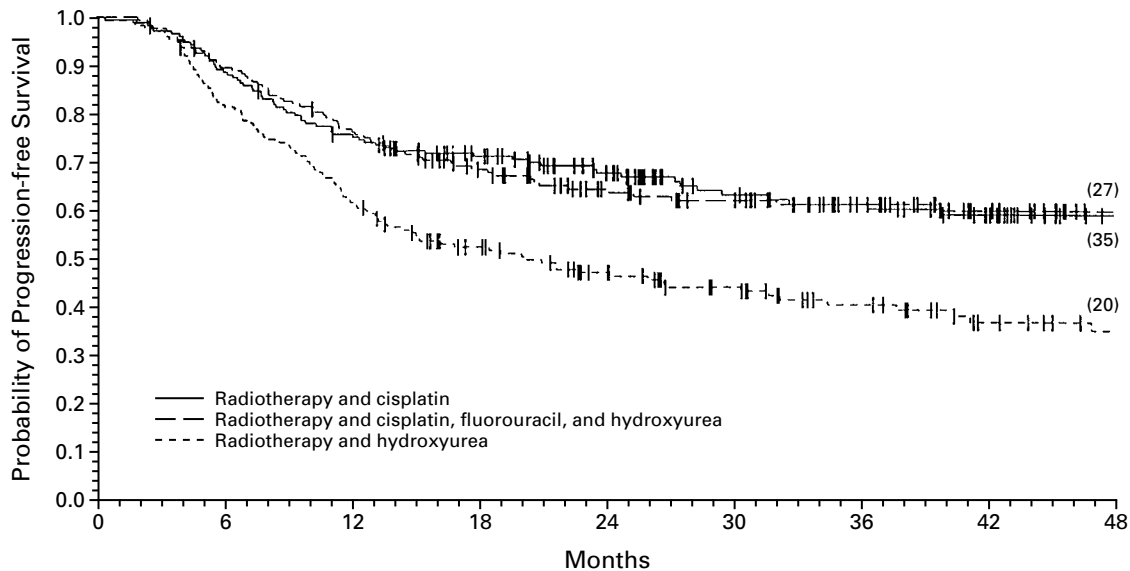
Figure 1. Kaplan–Meier Estimates of Progression-free Survival.

The rate of progression-free survival was significantly higher among patients in the group given radiotherapy combined with cisplatin therapy (109 of 176, P<0.001) and among patients in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea (106 of 173, P<0.001) than among patients in the group given radiotherapy combined with hydroxyurea therapy (73 of 177). Tick marks indicate patients with progression of disease. Numbers in parentheses are the numbers of patients at risk at four years.

Survival

The median duration of follow-up was 35 months. As of this writing, 75 percent of the patients have either died or have been followed for 30 months. A total of 205 patients have died (39 percent): 59 in the group given radiotherapy combined with cisplatin therapy; 57 in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 89 in the group given radiotherapy combined with hydroxyurea therapy. After adjustment for the clinical stage of disease, the relative risk of death was 0.61 (95 percent confidence interval, 0.44 to 0.85) in the group given radiotherapy combined with cisplatin therapy and 0.58 (95 percent confidence interval, 0.41 to 0.81) in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea, as compared with the group given radiotherapy combined with hydroxyurea therapy. Survival rates were also significantly better in these two groups (P=0.004 and P=0.002, respectively) than in the group given radiotherapy combined with hydroxyurea therapy (Fig. 2). A multivariate analysis of survival that was adjusted for the five prognostic factors identified by Stehman et al. yielded essentially identical estimates of relative risks.

Site of Progression

Patients in the group given radiotherapy combined with cisplatin therapy and the group given radiotherapy combined with treatment with cisplatin,

fluorouracil, and hydroxyurea had less local progression (19 percent and 20 percent, respectively) than those in the group given radiotherapy combined with hydroxyurea therapy (30 percent). Patients in the two cisplatin-treated groups also had a lower frequency of lung metastases (3 percent and 4 percent, respectively) than patients treated with hydroxyurea alone (10 percent).

Chemotherapy

Table 3 shows the number of cycles of chemotherapy (i.e., weeks) administered in each group.

Radiotherapy

Eight patients did not receive any radiation therapy, and 41 (8 percent) received only external-beam treatment, but these 49 patients were evenly distributed among the three treatment groups. The number of patients who received within 15 percent of the prescribed total dose to both point A (69 to 93 Gy) and point B (stage IIB, 47 to 63 Gy; stage III or IVA, 51 to 59 Gy) was 159 (90 percent) in the group given radiotherapy combined with cisplatin therapy; 147 (85 percent) in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 149 (84 percent) in the group given radiotherapy combined with hydroxyurea therapy.

The median duration of treatment was 9.0 weeks (10th and 90th percentiles, 7.1 and 11.9, respectively) in the group given radiotherapy combined with cis-
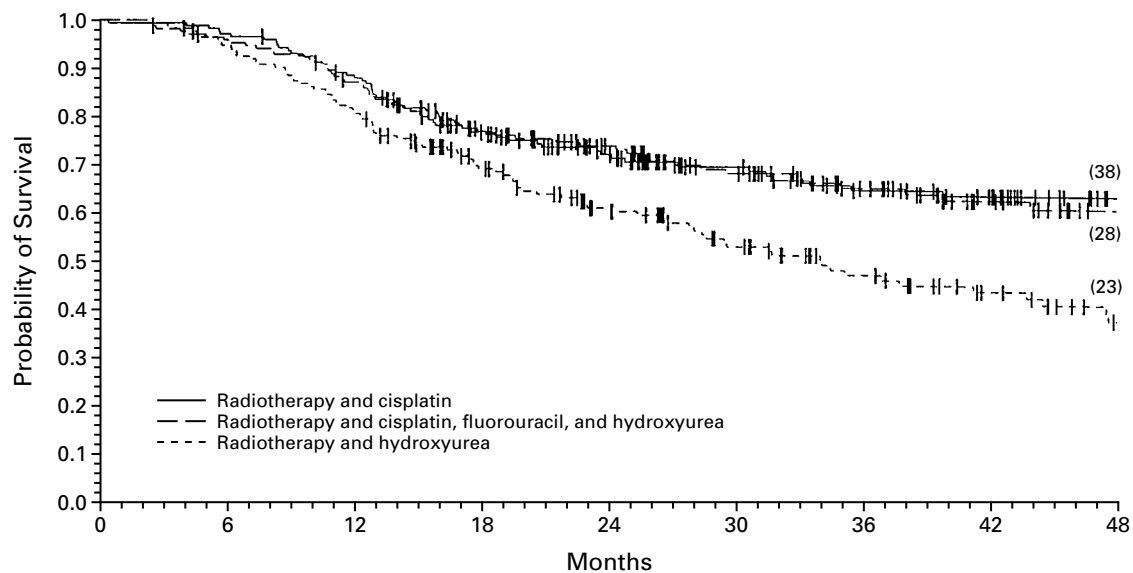
Figure 2. Kaplan–Meier Estimates of Overall Survival.
The overall survival rate was significantly higher among patients in the group given radiotherapy combined with cisplatin therapy (117 of 176, P=0.004) and among patients in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea (116 of 173, P=0.002) than among patients in the group given radiotherapy combined with hydroxyurea therapy (88 of 177). Tick marks indicate patients who died. Numbers in parentheses are the numbers of patients at risk at four years.

TABLE 3. NUMBER OF CYCLES OF CHEMOTHERAPY RECEIVED IN EACH GROUP.*

DRUG AND No. OF CYCLES	RADIOTHERAPY AND CISPLATIN (N=176)	RADIOTHERAPY AND CISPLATIN, FLUOROURACIL, AND HYDROXYUREA (N=173)	RADIOTHERAPY AND HYDROXY-UREA (N=177)
		no. of patients (%)	
Cisplatin			
0	1 (0.6)	3 (1.7)	—
1	2 (1.1)	29 (16.8)	—
2	2 (1.1)	140 (80.9)	—
3	7 (4.0)	1 (0.6)	—
4	18 (10.2)	—	—
5	59 (33.5)	—	—
≥6	87 (49.4)	—	—
Fluorouracil			
0	—	3 (1.7)	—
1	—	30 (17.3)	—
2	—	137 (79.2)	—
3	—	3 (1.7)	—
Hydroxyurea			
0	—	3 (1.7)	3 (1.7)
1 or 2	—	10 (5.8)	4 (2.3)
3	—	15 (8.7)	21 (11.9)
4	—	39 (22.5)	33 (18.6)
5	—	54 (31.2)	52 (29.4)
6	—	34 (19.7)	39 (22.0)
7	—	18 (10.4)	245 (14.1)

*Because of rounding, not all percentages total 100. Each cycle was one week.

platin therapy; 9.3 weeks (10th and 90th percentiles, 7.6 and 11.6) in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 8.9 weeks (10th and 90th percentiles, 7.2 and 11.2) in the group given radiotherapy combined with hydroxyurea therapy. The median delay in administering radiotherapy was computed for the 455 patients who received doses within 15 percent of the prescribed dose to both points A and B. The median delay was 8 days (the 10th percentile was a time 2 days ahead of schedule, and the 90th percentile was a delay of 22 days) in the group given radiotherapy combined with cisplatin therapy; 10 days (10th and 90th percentiles, 1 and 26) in the group given radiotherapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea; and 8 days (10th and 90th percentiles, 1 day ahead of schedule and a delay of 23 days) in the group given radiotherapy combined with hydroxyurea therapy.

Adverse Effects

There were no treatment-related deaths. The types and frequencies of adverse effects are shown in Table 4. The highest combined frequency of grade 3 (moderate) and grade 4 (severe) adverse effects was associated with treatment with radiotherapy and the three-drug regimen; the frequency in the other two groups was similar. The frequencies of both grade 3 and grade 4 leukopenia in the group given radio-

TABLE 4. ADVERSE EFFECTS.*

ADVERSE EFFECT	RADIOTHERAPY AND CISPLATIN (N=176)					RADIOTHERAPY AND CISPLATIN, FLUOROURACIL, AND HYDROXYUREA (N=173)					RADIOTHERAPY AND HYDROXYUREA (N=177)				
	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
							percentage of patients								
Leukopenia	34	17	26	21	2	8	9	37	41	5	18	8	53	20	1
Thrombocytopenia	79	15	4	2	0	73	22	2	3	1	92	7	1	1	0
Other hematologic effects	45	13	27	10	5	28	10	28	23	10	36	12	35	16	2
Gastrointestinal effects	28	32	28	8	4	26	24	31	9	9	35	29	22	10	4
Genitourinary effects	77	11	6	3	2	73	16	9	1	1	75	20	2	2	1
Cutaneous effects	85	7	6	1	1	77	10	7	3	2	80	10	6	3	1
Neurologic effects	85	6	8	1	0	89	6	3	1	0	90	5	3	1	1
Pulmonary effects	99	0	1	0	0	99	1	1	0	0	99	1	0	0	0
Cardiovascular effects	100	0	0	0	0	98	0	0	2	0	99	0	1	0	0
Fever	94	2	4	0	0	91	2	7	0	0	93	3	3	0	1
Fatigue	92	5	3	0	0	95	2	2	1	0	94	2	3	1	0
Pain	96	2	2	0	0	96	2	1	1	0	95	2	3	0	0
Weight loss	95	2	2	1	0	96	0	2	2	0	97	2	1	0	0
Hypomagnesemia	92	3	2	2	1	99	1	1	0	0	99	1	0	0	0
Other†	90	5	2	1	2	85	6	5	2	1	94	3	2	1	0

*A grade of 0 indicates the absence of an adverse effect, a grade of 1 a minimal effect, a grade of 2 a mild effect, a grade of 3 a moderate effect, and a grade of 4 a severe effect. Eight patients who did not receive radiotherapy were excluded from the analysis. Because of rounding, not all percentages total 100.

†This category includes grade 3 renal abnormalities (a serum creatinine level that was 3.1 to 6.0 times the institutional upper limit of normal; electrolyte imbalance; dehydration; and hepatic infection) and depression or anxiety and grade 4 lymphocytopenia, vaginal necrosis, renal abnormalities (a serum creatinine level that was more than 6.0 times the institutional upper limit of normal), and edema.

therapy combined with treatment with cisplatin, fluorouracil, and hydroxyurea were more than double the frequencies in the other two groups (P<0.001). The frequencies of other hematologic effects of both grade 3 and grade 4 — predominantly granulocytopenia — in the group given radiotherapy combined with cisplatin, fluorouracil, and hydroxyurea therapy were approximately double those in the other two groups (P<0.001).

DISCUSSION

Pelvic radiotherapy by itself fails to control the progression of cervical cancer in 35 to 90 percent of patients with locally advanced disease. Despite improvements in radiation equipment and techniques, in approximately two thirds of the cases, progression occurs within the area that was irradiated.[28,29] Thus, locoregional control must be improved. Since the para-aortic lymph nodes are often the first site of extrapelvic disease and involvement of these nodes was the most important prognostic factor in prior Gynecologic Oncology Group trials, only patients without involvement of the para-aortic lymph nodes were included in our study.[27]

We found higher rates of survival and progression-free survival among patients who were treated with radiotherapy and either cisplatin alone or cisplatin, fluorouracil, and hydroxyurea than among patients who were treated with radiotherapy and hydroxyurea alone. Cisplatin is believed to augment the effects of radiation by inhibiting the repair of radiation-induced sublethal damage and by sensitizing hypoxic cells to radiation.[9,30] Because of its cytotoxic effect, the drug reduces the bulk of tumors, which leads to reoxygenation of the tumor and entry of the cells into a radiation-sensitive phase of the cell cycle. In a study of 19 human cervical-cancer cell lines, Britten et al. found that radiotherapy and concomitant treatment with cisplatin increased the rates of death of these tumor cells.[31] However, radiosensitivity was increased in only four cell lines, suggesting that the effect of this combined therapy is primarily caused by direct cytotoxicity. The effects of chemotherapy should not interfere with the planned course of radiation, and one advantage of cisplatin is that it has limited adverse effects on bone marrow. In our study, the rate of local recurrences was significantly lower with either cisplatin-based regimen than with the hydroxyurea regimen, whereas the rate of distant recurrences, specifically in the lungs, was only slightly less. These results suggest that the principal effect of cisplatin is radiosensitization.

The effect of radiotherapy with concomitant treatment with cisplatin alone has been studied in several phase 2 trials.[16,18,32-40] Two trials reported improvements in local control of tumors and survival in pa-

tients with invasive bladder cancer and in patients with non–small-cell lung cancer.[41,42] However, in a small study of 45 patients with cervical cancer, radiotherapy and chemotherapy with cisplatin (25 mg per square meter per week) increased the rate of local control by 35 percent (P<0.025 for the comparison with radiotherapy alone), but there was no long-term improvement in survival.[14,43]

Many combinations of cisplatin have been studied in phase 2 trials of patients with cervical cancer.[44-51] In a phase 3 trial conducted by the Gynecologic Oncology Group, 388 patients were randomly assigned to receive radiotherapy and concomitant chemotherapy either with cisplatin and fluorouracil or with hydroxyurea (Whitney CW: unpublished data); the two-drug regimen improved survival (relative risk of death, 0.74; 95 percent confidence interval, 0.58 to 0.95). In the phase 3 study by Morris et al.,[52] whose results are reported in this issue of the *Journal*, radiotherapy in combination with treatment with cisplatin and fluorouracil significantly improved the rates of disease-free survival and overall survival among women with stage IB through IVA cervical cancer.

The ability of carboplatin, which is a less toxic analogue of platinum than cisplatin, to act as a chemosensitizer has been assessed in patients with many kinds of tumors.[53-59] Although cisplatin and carboplatin are often used interchangeably, we cannot assume that the results of our study also apply to treatment with carboplatin.

Hematologic toxicity was the principal adverse effect in this trial. The frequencies of grades 3 and 4 leukopenia were significantly higher with the three-drug combination than with the two single-drug regimens. Nevertheless, there were no significant differences in the length of radiotherapy among the three groups. Souhami et al. used radiotherapy concurrently with treatment with cisplatin, followed by high-dose brachytherapy, to treat 50 patients with cervical cancer.[39] They found a high rate of response, but 28 percent of their patients had severe late gastrointestinal complications. Closer analysis of this study showed a dose-dependent effect of the brachytherapy on late rectal complications.[60] Adverse urologic effects have occurred in mice treated with radiotherapy and chemotherapy with cisplatin,[61] but increased rates of urologic complications were not observed in our study.

The radiation protocol that we used allowed a total dose of 81 Gy to be delivered to point A and anticipated a total treatment time of 10 weeks. Several studies have suggested that the total length of treatment influences the efficacy of radiotherapy.[62-64] In our study, the duration of radiotherapy and the dose of radiation were similar among the three regimens, implying that the differences in progression-free survival and survival were related to the chemotherapy.

Our results demonstrate the superiority of radiotherapy and chemotherapy either with cisplatin alone or with cisplatin, fluorouracil, and hydroxyurea in patients with locally advanced cervical cancer (stage IIB, III, or IVA without metastasis to the para-aortic lymph nodes). Treatment with cisplatin alone was less toxic than treatment with the three-drug regimen. We recommend cisplatin as the standard drug for radiotherapy and chemotherapy for locally advanced cervical cancer.

APPENDIX

The following Gynecologic Oncology Group institutions participated in the study: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University School of Medicine, University of Minnesota Medical School, Emory University Clinic, 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, Milton S. Hershey School of Medicine of 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, Albany Medical College of Union University, University of California Medical Center at Irvine, Tufts–New England Medical Center, Rush–Presbyterian–St. Luke's Medical Center, State University of New York Downstate Medical Center, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Pennsylvania Hospital, Cooper Hospital University Medical Center, Columbus Cancer Council, University of Massachusetts Medical Center, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma Health Science Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, and New York Hospital–Cornell Medical Center.

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