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Chemoradiation Therapy for Cervical Cancer: Toxicity of Concurrent Weekly Cisplatin

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Purpose: To retrospectively evaluate the toxicity of concurrent weekly cisplatin and radiation therapy (RT) for locally advanced cervical cancer.

Materials and Methods: Between April 2001 and December 2004, 21 consecutive previously untreated patients with locally advanced cervical cancer were treated with concurrent chemoradiation therapy (CCRT) at the Tokushima University Hospital. Clinical stages were II: 5, III: 15, IVA: 1. External beam radiation therapy (EBRT) was delivered with 10 MV X-rays, 2 Gy fraction per day; total dose to the whole pelvis was 50 Gy. Iridium-192 high-dose-rate (HDR) intracavitary radiation therapy was performed with 10-30 Gy (median, 24 Gy) targeted at point A. Concurrent chemotherapy consisted of cisplatin, administered weekly at a dose of 40 mg/m^2 for patients who were younger than 65 years and 30 mg/m^2 for those 65 years or over. A maximum single dose of cisplatin, up to 70 mg/body, was administered in 5 cycles during EBRT.

Results: A total of 86 cycles of cisplatin were administered to the 21 patients, with a median of 4 cycles (range, 2-5). Severe hematological toxicity occurred in 18 patients (86%), including grade 3 in 17 patients (81%) and grade 4 in one patient (4.8%). Moderate or severe gastrointestinal toxicity occurred in 11 patients (52%), including grade 2 in 10 patients (48%) and grade 3 in one patient (4.8%). The grades of hematological toxicity were significantly greater in the 40 mg/m^2 group than in the 30 mg/m^2 group. All of the patients who were administered 40 mg/m^2 of cisplatin developed grade 3 or greater hematological toxicity, including one patient with grade 4 toxicity. In the 30 mg/m^2 group, 3 of 10 patients developed less than grade 3 toxicity, and all patients completed radiation therapy without interruption.

Conclusion: The incidence of severe acute hematological toxicity was significantly higher in this study than in previously reported randomized controlled trials (RCTs), especially in the group of 40 mg/m^2 cisplatin. A dose of 30 mg/m^2 of cisplatin was considered to be feasible in weekly cisplatin and radiation therapy.

Key words: radiation therapy, concurrent chemotherapy, cervical cancer, acute toxicity

Introduction

Despite advances in screening, cervical cancer remains a major health problem. In an effort to improve treatment results, both neo-adjuvant and concurrent chemoradiation therapy (CCRT) have been tried. Recently, five randomized controlled trials (RCTs)[1-5] have revealed significant survival advantages. In all trials, cisplatin-based chemotherapy (CT) administered concurrently with radiation therapy (RT) was the more effective therapy, reducing the risk of death by 30-50%. Acute toxicity, principally leukocytopenia and gastrointestinal, were more common with CCRT but were transient, and rates of late complications were similar between treatment groups. Based on the results of these 5 RCTs, in February 1999, the US National Cancer Institute (NCI) released a Clinical Announcement stating

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Table 1. Inclusion criteria

1. Patients with pathologically confirmed cervical cancer.
2. Clinical stage Ib2-IIa (tumor size: >4 cm in diameter) or IIb-IVa.
3. No previous treatment for cervical cancer.
4. Minimum life expectancy of 3 months.
5. Eastern Cooperative Oncology Group performance status 0 to 2.
6. Adequate function of the main organs (bone marrow, heart, lungs, liver, kidneys) required.
   White blood cell count (WBC) 4,000-12,000/mm^3, hemoglobin >9.5 g/dl, platelets >100,000/mm^3, serum total bilirubin <1.5 mg/dl, GOT, GPT <2×N (N: normal value), serum creatinine <1.5 mg/dl, creatinine clearance >50 ml/min, BUN <25 mg/dl.
7. Age 18-80 years.
8. Written informed consent obtained.

Table 2. Exclusion criteria

1. Existence of synchronous or asynchronous double primary malignancy.
2. Patients with the following complications.
   Acute infection.
   Severe heart disease, uncontrolled angina pectoris, myocardial infarction during the past 3 months.
   Uncontrolled hypertension or diabetes mellitus.
3. Known allergic reaction to cisplatin.

that the cisplatin-based CT that was used in these trials concurrently with RT should be the new standard of therapy for high-risk early stage and locally advanced cervical cancer. In Japan, there are no reports of RCT to evaluate CCRT for uterine cervical cancer. It is uncertain whether the same regimen as the RCTs is applicable to Japanese patients because of differences in the patient age distribution and RT procedures. In the RCTs, the median age of patients was 41-47 years,[1,5] and elderly patients over 70 years were enrolled only 3%[2-4] of the time. CT and external beam radiation therapy (EBRT) were performed concurrently, followed by low-dose-rate (LDR) brachytherapy. In the present study, we assessed the compliance and toxicity of concurrent weekly cisplatin and RT using high-dose-rate (HDR) brachytherapy.

Patients and Methods

Patients

Eligibility criteria and exclusion criteria for patients who had undergone concurrent cisplatin and RT are shown in Tables 1 and 2. Between April 2001 and December 2004, a total of 22 patients who conformed to the criteria underwent CCRT as routine treatment at Tokushima University Hospital. Written informed consent was obtained from all patients. We retrospectively evaluated the clinical results of 21 patients. One patient who was not followed up at our institution was excluded from this study. The distribution of age, clinical stage, and pathological findings are presented in Table 3. All patients underwent clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) criteria.[6] Staging was performed in all cases through cystoscopy, romanoscopy, computed tomography, and magnetic resonance imaging. Tumor size was measured on T2-weighted images of MRI.

Radiation therapy

EBRT was performed with 10 MV X-rays using the anterior posterior parallel opposing field technique. Five fractions weekly, of 2.0 Gy per fraction, were delivered to the mid-plane of the pelvis. A total dose of 50 Gy was administered to the whole pelvis with 3-cm center shielding at 20-30 Gy (median, 30 Gy). Intracavitary RT using HDR brachytherapy was started 7-21 days after the first day of EBRT. HDR brachytherapy was delivered by a remotely controlled after-loading system, MicroSelectron (Nulcetron, Veenendaal, Netherlands). The system contained a high-activity Ir-192 source (360 GBq at time of installation). Source loading corresponded to the Manchester system for uterine cervical cancer.[7] HDR brachytherapy and EBRT were never given on the same day. The computerized planning program used the PLATO system version 3.4 (Nucletron,

Table 3. Patient characteristics

Age (years): median (range)		70 (45-79)
Performance status	0-1	21
	2	0
Clinical stage	Ib	0
	IIa	1
	IIb	4
	IIIb	15
	IVa	1
Tumor size (cm): median (range)		5 (3-9)
Pretreatment Hb (mg/dl): median (range)		11.3 (9-14)
Histology: squamous cell carcinoma		19
adenocarcinoma		2
Follow-up period (months): median (range)		18 (3-46)

Table 4. Summary of acute toxicity grading according to CTC of NCI

Toxicity grading	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal				
Anorexia/nausea	Loss of appetite	Unable to eat but can drink	Requiring IV fluids	Requiring feeding tube
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	≧6 episodes in 24 hours	Requiring intensive care
Diarrhea	Increase of <1 stool/day	Increase of 1-6 stools/day	Increase of ≧7 stools/day	Requiring intensive care
Hematological				
White blood cells	<LLL-3,000/mm^3	2,000- <3,000/mm^3	1,000- <2,000/mm^3	<1,000/mm^3
Hemoglobin	<LLL-10.0 g/dl	8- <10.0 g/dl	6.5- <8.0 g/dl	<6.5g/dl
Platelets	<LLL-75,000/mm^3	50,000- <75,000/mm^3	20,000- <50,000/mm^3	<20,000/mm^3

CTC, common toxicity criteria; NCI, National Cancer Institute; IV, intravenous; LLL, lower limit of normal value.

Veenendaal, Netherlands). A total dose of 20-27 Gy (median, 24 Gy) was delivered to point A, defined by the Manchester system as 2 cm above the opening of the uterus and 2 cm lateral from the midline. Intracavitary RT was administered once a week with a daily fraction size of 5.0-6.0 Gy (median, 6.0 Gy). EBRT was withheld if the white blood cell count fell below 1,000/mm^3 or if platelets fell below 50,000/mm^3 and was resumed once the count rose above those levels.

Chemotherapy

CT consisted of cisplatin administered weekly at a dose of 40 mg/m^2 for patients under 65 years of age and 30 mg/m^2 for those 65 or over. A maximum single dose of cisplatin up to 70 mg/body, was administered in 5 cycles during EBRT. Beginning the day before CT, continuous intravenous infusion of Glucose-Ringer's solution was given for three days to maintain hydration. Fosfomycin at 2 g twice a day and 300 ml of D-mannitol were administered in order to prevent renal function. Granisetron (3 mg) was routinely administered on the day of CT as an anti-emetic treatment, and 8 mg of dexamethasone was added for patients who complained of severe nausea. CT was withheld if grade 3 or greater gastrointestinal toxicity appeared, the total white blood cell count fell below 3,000/mm^3, or if platelets fell below 100,000/mm^3 and was resumed once the count rose above those levels. Colony-stimulating growth factors were used if neutrophils fell below 500/mm^3 or if total white blood cell count fell below 1,000/mm^3.

Toxicity

Toxicity was assessed weekly throughout treatment and graded according to the NCI Common Toxicity Criteria,[8] and late radiation morbidities were graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme[9] (Table 4). Regular check-ups were done monthly for one year after the completion of radiation therapy and every three months thereafter. The median follow-up period was 18 months (range, 3-46 months).

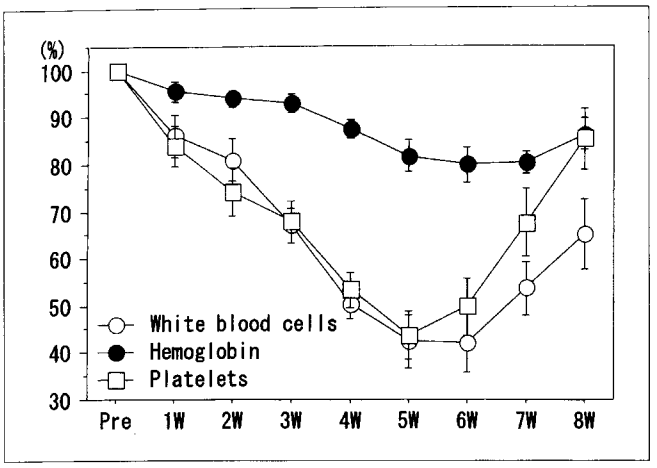

Fig. 1. Changes in acute hematological toxicity. Error bars indicate standard deviation of the mean.

Table 5. Acute toxicity according to CTC of NCI

Toxicity grading	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal					
Anorexia/nausea	1	9	10	1	0
Vomiting	10	8	2	1	0
Diarrhea	10	7	4	0	0
Hematological					
White blood cells	1	0	3	16	1
Hemoglobin	0	4	10	7	0
Platelets	6	9	4	2	0

CTC, common toxicity criteria; NCI, National Cancer Institute.

Statistics

The Mann-Whitney U-test was used to compare toxicity data between other reports and the present study, and Spearman's rank correlation test was used to compare toxicity data between groups treated with 30 mg/m^2 and 40 mg/m^2 of cisplatin. Differences were considered significant at $p<0.05$. Analyses were done using Stat View 5.0 (SAS Institute, Cary, USA).

Results

Grade 3 or greater hematological toxicity occurred in 18 patients (86%), including one grade 4 leukocytopenia case. The nadir of leukocytopenia was observed during the fourth or fifth week in 8 patients and the sixth or seventh week in 13 patients. Granulocyte-stimulating factor was delivered to12 patients (Fig. 1). Grade 1 or 2 gastrointestinal toxicity occurred in 19 patients (90%), and grade 3 gastrointestinal toxicity occurred in one patient; however, these were usually transient and disappeared within 2 or 3 days after the administration of cisplatin (Table 5). The number of cisplatin cycles delivered was 2 in one patient, 3 in three patients, 4 in ten patients and 5 in seven patients. One patient who was delivered 40 mg/m^2 of cisplatin was not able to continue CT after 2 cycles owing to grade 3 gastrointestinal toxicity. Three of 21 patients were also delivered only 3 cycles of cisplatin owing to hematological toxicity. Neuronal toxicity and urinary toxicity were not observed in any patients, although one patient required a 17-day interruption and platelet transfusion because of hematological toxicity. The treatment period was 36-61 days (median, 44 days) and hospitalization was necessary for 38-85 days (median, 63 days).

All of the patients who received 40 mg/m^2 cisplatin developed grade 3 or greater hematological toxicity, including one patient with grade 4 toxicity (Table 6). In the 30 mg/m^2 group, 3 of 10 patients developed less than grade 3 toxicity, and no patients developed grade 4 toxicity. The grades of hematological and gastrointestinal toxicity were significantly greater in the 40 mg/m^2 group than in the 30 mg/m^2 group.

Severe late radiation morbidity was not observed in any patients with a median follow-up period of 18 months. Grade 1 proctitis occurred in two patients at 6 and 8 months, respectively, after RT, and two patients had developed insufficient pelvic bone fractures within one year after RT.

Discussion

Cisplatin is the most effective cytotoxic agent against cervical cancer in single-drug CT. The CT regimen of all five RCTs contained cisplatin as a key drug. However, regimens of CT varied, and the total doses of cisplatin administered in the treatment of the five RCTs ranged from 100-240 mg/m^2. The optimal cisplatin dose in combination with RT and 5-fluorouracil is still debatable. The regimen in which the cisplatin dose was greatest was weekly administered cisplatin in the Gynecologic Oncology Group (GOG) Trial 120[2] and GOG Trial 123.[3] GOG Trial 123 demonstrated the equivalence of cisplatin alone and cisplatin combined with 5-fluorouracil, with greater toxicity occurring in the latter. According to the results of GOG trials, a combination of weekly 40 mg/m^2 of cisplatin and RT was adapted as a routine regimen in our institution. However, the GOG trials and the present study differed in the distribution of patient age. Although elderly patients over 70 years old accounted for only 4% in GOG Trial 120 and 2.3% in GOG Trial

Table 6. Number of cisplatin cycles and acute toxicity according to dose of cisplatin

	Dose of cisplatin		p-value
	30 mg/m^2	40 mg/m^2	
Number of cisplatin cycles			
2	0	1	
3	1	2	
4	6	4	
5	3	4	<0.01
Hematological toxicity			
Grade 1	1	0	
Grade 2	2	0	
Grade 3	7	10	
Grade 4	0	1	<0.01
Gastrointestinal toxicity			
Grade 0	1	0	
Grade 1	5	4	
Grade 2	4	6	
Grade 3	0	1	<0.01
Total number of patients	10	11	

p indicates significance of Spearman rank correlation test.

Table 7. Acute toxicity of concurrent chemoradiation therapy using weekly cisplatin according to CTC of NCI

	Rose *et al.* (GOG120)[2] (n=176) (%)	Keys *et al.* (GOG123)[3] (n=183) (%)	Strauss *et al.*[14] (n=27) (%)	Present study (n=21) (%)	p-value (vs. present study)
Hematological	NR		NR		<0.01
Grade 1		20		5	
Grade 2		36		9	
Grade 3		18		81	
Grade 4		3		5	
Leukopenia		NR			<0.01
Grade 1	17		33	0	
Grade 2	26		33	14	
Grade 3	21		30	76	
Grade 4	2		0	5	
Thrombocytopenia		NR			<0.01
Grade 1	15		22	43	
Grade 2	4		0	19	
Grade 3	2		0	10	
Grade 4	0		0	0	
Gastrointestinal			NR		*0.1795
Grade 1	32	31		43	**0.2263
Grade 2	28	27		52	
Grade 3	8	9		5	
Grade 4	4	5		0	

NR, not reported.
p indicates significance of Mann-Whitney's U-test.
*, GOG120 vs. present study; **, GOG123 vs. present study.

Table 8. Number of cisplatin cycles delivered during chemoradiation therapy

Author/Ref. no.	Number of patients	Brachytherapy	Cisplatin	Number of cisplatin cycles (%)					
				1	2	3	4	5	6
Souhami *et al.*[12]	50	HDR	30 mg/m^2				≧4: 92		
Rose *et al.*[2]	176	LDR	40 mg/m^2	0.6	1.1	4	10.2	33.5	49.4*
Keys *et al.*[3]	183	LDR	40 mg/m^2				≧4: 90		
Abu-Rustum *et al.*[13]	65	LDR	40 mg/m^2	1.5	3.1	4.6	20	60	10.8
Strauss *et al.*[14]	13/14**	HDR	40 mg/m^2	0	0	3.7	14.8	14.8	66.7
Serkies *et al.*[15]	57/55**	LDR/MDR	40 mg/m^2	7.1	5.4	13.4	29.5	38.4	6.2
Present study	21	HDR	30/40 mg/m^2	0	4.8	14.2	47.6	33.3	—

HDR, high-dose-rate; LDR, low-dose-rate; MDR, middle-dose-rate.
*, Six or more cycles of cisplatin; **, definite radiation therapy/postoperative radiation therapy.

123, more than half of the patients in our institution were over 65 years old. The dose of cisplatin was reduced to 30 mg/m^2 for patients over 65 years old in our regimen because bone marrow and renal function were considered to be deteriorated owing to aging.

A systematic review and meta-analysis[10,11] reported that grade 3 or 4 hematological toxicity was significantly greater in the CCRT group than the control group (odds ratios of white blood cell count and platelets were 2.15-2.21 and 3.04-3.73, respectively). In GOG Trial 120, grades 3 and 4 leukocytopenia occurred in 21% and 2% of patients, respectively. In GOG Trial 123 using preoperative EBRT and brachytherapy combined with weekly cisplatin, grades 3 and 4 hematological toxicity were observed in 18% and 3% of patients, respectively, compared with 2% moderate hematological toxicity, respectively, in the group assigned to RT alone. In the present study, grades 3 and 4 hematological toxicity were observed in 81% and 5%, respectively, significantly higher than in the groups treated with CCRT using weekly cisplatin in the GOG trials. Although all patients completed RT in the present study, only 33% of patients could receive five cycles of cisplatin due to severe hematological toxicity. This result is lower than the previous reports from American and European institutions.[2,3,12-15] In GOG Trial 120, 49.4% of patients were delivered 6 or more cycles of cisplatin (Table 8).

A systematic review and meta-analysis[10,11] reported that grade 3 or 4 gastrointestinal toxicity was also significantly greater in the CCRT group than the control group (odds ratio of gastrointestinal toxicity, 1.92-2.22). In GOG Trial 120, grades 3 and 4 gastrointestinal toxicity developed in 8% and 4% of patients, respectively. In GOG Trial 123, grades 3 and 4 gastrointestinal toxicity were observed in 9% and 5% of patients, respectively, compared with 2% and 3% moderate and severe gastrointestinal toxicity, respectively, in the group assigned to RT alone. In the present study, grades 3 and 4 gastrointestinal toxicity were observed in 5% and 0%. There was no significant difference between the present study and the GOG trials.

It was reported that there was no significant difference in the incidence of late radiation morbidities in the RCTs. In the present study, no severe late complications were observed. However, this cannot be concluded because the follow-up period was insufficient, and more prolonged follow-up is necessary.

Administration of full-dose CT was difficult in many patients treated with CCRT using weekly 40 mg/m^2 of cisplatin because of hematological toxicity, although the delivery of planned radiation therapy was not compromised. The differences in radiation procedure and age distribution of patients are regarded as important factors in the results of acute hematological toxicity between RCTs and the present study. HDR brachytherapy was started within the treatment period of EBRT in our institution, but LDR brachytherapy was usually delivered after EBRT in the RCTs. Half of the patients in the present study were over 65 years old, and it was considered that bone marrow function had deteriorated due to aging.

There was a significant difference in hematological toxicity between the groups delivered 30 mg/m^2 and 40 mg/m^2 of cisplatin. The patients in the 30 mg/m^2 group had less hematological toxicity and more delivered cycles of cisplatin. Although the efficacy of concurrent use of weekly 30 mg/m^2 of cisplatin is uncertain especially for advanced cervical cancer, Ohara *et al.* reported significant findings, namely, results that estimate tumor regression rate and suggest that concurrent weekly 30 mg/m^2 doses of cisplatin heighten the radioresponse of large-size cervical cancer.[16] In our institution, weekly cisplatin doses of 30 mg/m^2, tolerable even for elderly patients, have been implemented as a routine regimen in CCRT for locally advanced cervical cancer.

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