Low Dose Cisplatin as a Radiation Sensitizer in Management of Locally Advanced Squamous Cell Carcinoma of the Uterine Cervix:Evaluation of Acute Toxicity and Early Response

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Purpose: To evaluate possible acute toxicity and early response of concurrent radiation therapy and low dose daily cisplatin as a radiosensitizer in patients with locally advanced uterine cervical carcinomas.

Materials and Methods: From December 1996 to January 1999, 38 previously untreated patients with locally advanced squamous cell carcinoma of the uterine cervix (from stage IIB to stage IIIB) were treated at Inha University Hospital. All patients underwent standard pretreatment staging procedures after the initial evaluation by gynecologists and radiation oncologists. Sixteen patients with huge cervical mass (>4 cm) were submitted to the group treated with concurrent radiation therapy and low dose daily cisplatin while the remainder was treated with radiation therapy alone. Radiation therapy consisted of 4500 cGy external beam irradiation to whole pelvis (midline block after 3060 cGy), 900 1000 cGy boost to involved parametrium, and high dose-rate intracavitary brachytherapy (a total dose of 3000 3500 cGy/500 cGy per fraction to point A, twice per week). In the group treated with low dose cisplatin concurrently, 10 mg of daily intravenous cisplatin was given from the 1st day of radiation therapy to the 20th day of radiation therapy. Acute toxicity was measured according to expanded common toxicity criteria of the NCI (C) Clinical Trials. Early response data were analyzed at minimum 4 weeks' follow-up after completion of the treatment protocol.

Results: Hematolgic toxicity was more prominent in patients treated with radiation therapy and cisplatin. Six of 16 patients (37.5%) treated with radiation therapy and cisplatin and one of 22 patients (4.5%) treated with radiation therapy alone experienced grade 3 leukopenia. In Fisher's exact test, there was statistically significant difference between two groups regarding leukopenia (P=0.030). There was no apparent difference in the frequency of gastrointestinal and genitourinary toxicity between two groups (P=0.066). Three of 16 patients (18.7%) treated with radiation therapy and cisplatin and two of 22 patients (9.1%) treated with radiation therapy alone experienced more than 5 kg weight loss during the treatment. There was no statistically significant difference on weight loss between two groups (P=0.63). Two patients on each group were not evaluable for the early response because of incomplete treatment. The complete response rate at four weeks' follow-up was 80% (16/20) for the radiation therapy alone group and 78% (11/14) for the radiation therapy and cisplatin group. There was no statistically significant difference in early response between two treatment groups (P=0.126).

Conclusion: This study led to the conclusion that the hematologic toxicity from the treatment with concurrent radiation therapy and low dose daily cisplatin seems to be more prominent than that from the treatment of radiation therapy alone. There was no grade 4 hematologic toxicity or mortality in both groups. The hematologic toxicity in both treatment groups seems to be well managable medically. Since the risk factors were not balanced between two treatment groups, the direct comparison of early response of both groups was not possible. However, preliminary results regarding early response for patients with bulky cervical tumor mass treated with radiation therapy and low dose daily cisplatin was encouraging. Longer follow-up is necessary to evaluate the survival data. A phase III study is needed to evaluate the efficacy of concurrent daily low dose cisplatin with radiation therapy in bulky cervical cancer.

Key Words: Cervical cancer, Concurrent chemoradiotherapy, Radiation sensitizer

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INTRODUCTION

Radiation therapy (RT) alone is currently considered as the standard treatm

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ent for patients with locally advanced cervical carcinoma. Despite the introduction of megavoltage machines and the improved brachytherapy techniques, locally advanced cervical cancer patients with a huge cervical mass treated with radiation treatment alone have shown a high rate of local recurrences and distant metastases. This has led to the investigation of a number of alternative approaches designed to increase the radiation effect such as radiation treatment with hypoxic cell sensitizers,2) hyperbaric oxygen,3) and adjuvant chemotherapy.4,5) However, these treatment modalities published to date demonstrated very limited success and sustained improvement in terms of pelvic control or survival rate. Therefore, new and innovative therapeutic approaches are clearly needed.

The study conducted by the European Organization for Research and Treatment of Cancer (EORTC) for advanced lung cancer disclosed significant benefits for patients treated with concurrent radiotherapy and daily low dose cisplatin (daily 10 mg/m2) compared to those of patients treated with radiotherapy alone or concurrent radiotherapy and weekly cisplatin.6) Based on these data, the feasibility study of daily low dose cisplatin as a radiation sensitizer with pelvic radiation therapy for patients with locally advanced cervical carcinoma is designed to analyze the early response and acute toxicity of this regimen in comparison to those of radiation therapy alone.

MATERIALS AND METHODS

1. Patient Entry Criteria and Evaluation

From December 1996 to January 1999, 38 previously untreated patients with carcinoma of the cervix were entered in the study. Eligible criteria included FIGO stage IIB to IIIB, histopathologic confirmation, no previous history of malignancy, and performance status greater than 70 on the Karnofsky scale. Adequate bone marrow reserve and normal renal and liver functions were requisites for entry into the study. The international Federation of Gynecology and Obstetrics (FIGO) staging criteria were used. Initial pelvic examination was performed by a gynecologist and a radiation oncologist. Staging evaluation included a physical examination, cystoscopy, chest X-ray, computer tomography (CT) scan of the abdomen and pelvis, MRI of the pelvis, complete blood counts and blood chemistries. Patients with suspicious para-aortic lymph nodes on CT of the abdomen and pelvis were excluded from the study.

Table 1. Patient Characteristics (total number=38)

	Characterics	
	RT alone	RT＋cisplatin
Total No. of patients studied	22	16
Age (years)		
Median	61	55
Range	40 86	35 75
Histology		
Squamous	21	14
Adenocarcinoma	0	1
Adenosquamous	1	1
FIGO stage		
IIB	21	15
IIIB	1	1
Tumor size		
<4	9	0
4.0 4.9	8	8
5.0 5.9	2	6
>6.0	3	2
Pelvic LN		
Negative	15	9
Positive	7	7

Patient's characteristics are outlined in Table 1. These groups were not balanced in terms of tumor size. There were more patients with bulky (>4 cm) cervical mass in concurrent radiation therapy (RT) and low dose cisplatin (cisplatin) group than those in radiation therapy (RT) alone group (P=0.0137).

2. Treatment Regimens

Patients were grouped as RT alone group and concurrent RT and cisplatin group after the completion of staging procedures. The external beam radiation therapy (EBRT) was administered using an isocentric set-up and a four field box technique on a 10 MV photon linear accelerator. The superior margin of the radiation field was the L5-S1 junction, the lower margin was the caudal pole of obturator foramen, and the lateral boundaries were 1.5 cm outside of pelvic sidewalls. Patients were treated on prone position with a full bladder. A dose of 3060 cGy was delivered in 5 days a week at 180 cGy per fraction. After this, midline block was added up to 4500 cGy using parallel opposed anterior and posterior ports. Parametrial boost up to 5400 cGy was administered to the involved side (s).

Intracavitary radiotherapy was given using a high dose-rate (Ir-192 source) remote afterloading unit following 3060 cGy external beam radiotherapy (EBRT), once a week while receiving EBRT and twice a week after finishing EBRT to a total dose of 3000 cGy prescribed at point A in six insertions of 500 cGy each.

Cisplatin was administered as intravenous bolus 30 minut es before the irradiation at a daily dose of 10mg from the first day of EBRT to 20th day of EBRT on an

outpatient basis except for one patient who wished to be treated as an inpatient.

3. Evaluation Criteria

Early response to the treatment were evaluated by pelvic examination and appropriate imaging studies. Response data were gathered and analyzed at 4 weeks' follow-up after completion of treatment protocol. A complete remission (CR) was defined as the complete resolution of all measurable disease and a partial response was defined as a 50% reduction of the initial tumor size.

Acute toxicity was measured and recorded according to expanded common toxicity criteria of the NCI (C) Clinical Trials.

During the course of radiation therapy, patients were assessed and recorded weekly regarding the presence of treatment related symptoms. Blood counts were checked and recorded weekly as well.

4. Statistical Analysis

The Fishers exact test was used for the comparison of variables between RT alone group and concurrent RT and cisplatin group.

RESULTS

1. Early Response

Evaluation of early response was possible in 34 patients (20 patients of RT alone group and 14 patients of concurrent RT and cisplatin group) out of 40 patients treated following the protocol, since four patients had less than four weeks of follow-up after the completion of treatments and two patients gave up further treatment after one week of radiation treatment due to financial or personal problems.

Table 2 shows the early response for the two regimens. The complete response rate at four weeks' follow-up was 80% for the RT alone group and 78% for concurrent RT and cisplatin group. There was no statistically significant difference in early response to each treatment group by Fisher's exact test (P=0.126).

Table 2. Comparision of Early Response by Treatment Regimen (total number=34)

	RT alone (n=20)	RT+cisplatin (n=14)
	No. (%)	No. (%)
Complete Response (CR)	16 (80)	11 (78)
Partial Response (PR)	4 (20)	3 (22)

2. Acute Toxicity

Treatments were generally well tolerated and no patient required a treatment break for more than one week because of acute toxicity. Two patients of concurrent RT and cisplatin group who refused further radiation treatment after one week of radiation treatment were excluded from the analysis of acute toxicity. Table 3 shows acute hematologic toxicities of both groups. No grade 4 acute toxicities were observed. Hematolgic toxicity was more prominent in the concurrent RT and cisplatin group. Six of the sixteen patients (37.5%) treated with concurrent RT and cisplatin and one of the twenty two patients (6.2%) treated with RT alone experienced grade 3 leukocytopenia. In Fisher's exact test, there was statistically significant difference between the two groups regarding leukocyte count (P=0.030). But these grade 3 leukocytopenia patients recovered to the level of more than 2000/L of leukocyte count after 3 or 4 days' rest and the treatments could be resumed with no more than one week's rest. Platelet count, hemoglobin, and hematocrit showed less than grade 3 acute toxicity.

Table 3. Acute Hematologic Toxicity (total number=38)

	1		2		3	
Toxic effect	RT alone	RT+cisplatin	RT alone	RT+cisplatin	RT alone	RT+cisplatin
Leukocyte	6	4	4	5	1	6
Platelet	0	5	0	2	0	0
Hg	6	10	3	7	0	0
Hct	7	10	0	0	0	0

Table 4. Acute Gastrointestinal and Gentourinary Toxicity (total number=38)

Grade	1		2		3	
toxic effect	RT alone	RT＋cisplatin	RT alone	RT＋cisplatin	RT alone	RT＋cisplatin
Nausea/Vomiting	5	4	2	8	0	3
Diahrrea	8	5	2	3	0	0
Abd. Pain	8	6	2	1	0	1
Urinary frequency	1	1	0	0	0	0
Dysuria	1	1	0	0	0	0
Tenesmus	5	1	1	4	0	0

Table 4 shows acute gastrointestinal and genitourinary toxicities. One patient in the concurrent RT and cisplatin group experienced grade 3 nausea and vomiting which was controlled easily with ondansetron. Only one patient in the concurrent RT and cisplatin group was hospitalized because of a grade 2 diarrhea but continued radiation therapy after fluid therapy. One patient experienced a grade 3 abdominal pain but she resumed the treatments after 3 days' rest. There was no statistically significant difference in the frequency of gastrointestinal and genitourinary toxicity. In Fisher귕 exact test, there was no significant difference in nausea and vomiting (P=0.066).

Three of the sixteen patients (18.7%) in the concurrent RT and cisplatin group and two of the twenty-two patients (9.1%) in the RT alone group experienced more than 5 kg weight loss during the treatments as shown on Table 5. There was no statistically significant difference on weight loss in Fishers exact test (P=0.63).

Table 5. Weight Loss During Treatment (total n=38)

Weight loss	RT alone	RT＋cisplatin
Nill	7	9
<5 kg	4	2
5 10 kg	13	3

DISCUSSION

The majority of patients with locally advanced carcinoma of the uterine cervix which are not cured usually die with uncontrollable local disease in the pelvis.1) Even in the presence of metastatic disease, local relapse may produce symptomatic problems including pain, fistulae and leg edema. Since the addition of surgery or conventional chemotherapy has not altered this significantly, it would appear that the investigation of radiation sensitizing agents in the management of this disease is advisable.

Cisplatin has been shown to have modest advantage in advanced, metastatic, or recurrent carcinoma of the uterine cervix.7) It forms covalent links between platinum and DNA, RNA, and other proteins; these crosslinks give rise to critical lesions in the presence of radiation.8) Cisplatin, given before irradiation, causes an increase in the slope of the radiation dose-response curve. Experimental data suggest that the antitumor activity may be greater if cisplatin is administered by continuous infusion. In addition, with continuous infusion, thiphasic decay of the drug occurs with terminal half-life of 24 hours.10) Some complications such as nephrotoxicity can be reduced with continuous infusion.

This study was based on the report from Schaake-Koning et al.,6) where significant survival benefit was displayed in patients treated with RT plus daily low-dose cisplatin (6 mg/m2 before each radiation fraction) for locally advanced non-small cell carcinoma of the lung with the European Organization for Research and Treatment of Cancer (EORTC). Before the phase III study that compares survival rate and late toxicity, we have assessed the early response and acute toxicity of daily low dose cisplatin with concurrent radiation therapy compared to those of radiation therapy alone to evaluate the feasibility of this regimen for locally advanced carcinoma of the uterine cervix. Although the two groups were not balanced in terms of the tumor size, since all patients in the concurrent RT and cisplatin group had bulky cervical mass of more than 4 cm and only 59% of patients in RT alone group had bulky cervical mass of more than 4 cm (P=0.0137), our study revealed that the early responses in both groups were similar. This may indicate that concurrent RT and cisplatin regimen may improve local control for patients with bulky cervical tumor.

Choo and associates11) treated 45 patients in a randomized study with either radiation or radiation plus cisplatin. Cisplatin was administered weekly at a dose of 25 mg/m2. At the time of first intracavitary implant, a complete response was noted in 55% of those treated with chemoradiotherapy, but it was noted in only 20% of those treated with radiation alone. The other small series of studies reported by Piver and associates12) include nine patients, all with extensive paraaortic lymph node metastatsis. A complete response was noted in 78% and a partial response was noted in 32% but there was no

increase in 5-year survival rate.

Micheletti et al.13) reported a phase II trial to assess the efficacy and local toxicity of the combination of low doses of cisplatin and pelvic radiotherapy in patients with locally advanced carcinoma of the cervix. Nine patients were classified as stage IIB and 14 patients as stage IIIB. 60 Gy external beam irradiation (46 Gy to pelvis + 14 Gy boost to cervix uteri and parametria) plus one low dose rate intracavitary treatment to a dose of 8 Gy to point A was given. Cisplatin (3 mg/m2/day) or carboplatin (12 mg/m2/day) was also given for 6 weeks starting on the first day of radiotherapy. The treatment was well tolerated and no patient required radiotherapy discontinuation. Complete response was seen in 74% (17/23) of the patients. Actuarial overall and disease-free survival rates at 33 months were 69.1% and 65.2%, respectively. The combination of cisplatin and radiotherapy appears to be an effective regimen for the patients with locally advanced carcinoma of the cervix and caused a relatively low rate of late gastrointestinal complications. Hus WL et al.14) treated 30 patients with Stage IIIB cervical cancers using synchronous radiotherapy, 5-fluorouracil (5-FU), and daily low-dose cisplatin. Continuous infusion of 5-FU 750 mg/m2 was given for 5 days during the first and third week of pelvic irradiation. Cisplatin (6 mg/m2) was given 30 min before every irradiation in the second and fourth week. The complete response rate was 87%. The 3-year local control rate was 77%. The 3-year overall and disease-free survival rate was 66% and 56%, respectively. Toxicities were acceptable. This preliminary result indicates that this synchronous combination treatment is feasible.

It is apparent that radiation therapy alone is not successful in producing prolonged survival in a significant number of patients with bulky primary lesions.15) In this study, the radiation therapy and concurrent use of cisplatin as a radiation sensitizer, although the majority of patients with bulky cervical mass were in the concurrent RT and cisplatin group, showed similar early response rate compared with the radiation therapy alone. This result may indicate that the simultaneous administration of low dose daily cisplatin as a radiation sensitizer is a moderately effective regimen.

The major toxicity was hematologic. Five of the eleven patients (54.4%) in concurrent RT and cisplatin group and one of the sixteen patients (6.2%) in RT alone group had leukocyte counts of less than 2000/mm2. Treatment was temporarily suspended at these stages. After 3 4 days' rest, the leukocyte counts were recovered to a normal value. Historically the treatments with radiotherapy alone have reported a 0 2% incidence of leukopenia and thrombocytopenia.16) No mortality or life-threatening complications were associated with these hematologic toxic reactions.

CONCLUSION

This study led to the conclusion that the hematologic toxicities of daily low dose cisplatin with concomitant radiation therapy seemed more prominent than those of radiation therapy alone. There was no grade 4 hematolgic toxicities or mortality in either group. The hematologic toxicity in both treatment groups was medically managable. The concomitant administration of daily low dose cisplatin does not seem to compromise the delivery of standard dose of radiation therapy. Since the risk factors such as mass size were not balanced in two treatment groups, the direct comparision of early response of both group was not possible. However early complete response was similar in both groups despite all the patients in concurrent RT and cisplatin group had bulky cervical mass while only one half of the RT alone group had bulky cervical mass. This preliminary results indicate that concurrent RT and cisplatin regimen may improve local control for high risk patients with bulky cervical mass.

The number of patients was too small and follow-up period was too short to evaluate the survival rate in this study. Since the risk factors were not balanced, we could not compare the early response of both groups directly. But preliminary results are encouraging for patients with bulky cervical mass treated with concurrent RT and cisplatin. Longer follow-up is necessary to evaluate the survival data. A phase III study is needed to evaluate the efficacy of daily low dose cisplatin with concomitant radiation therapy in management of bulky cervical cancer.

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국문 초록

국소 진행된 자궁경부암의 방사선치료와 저용량 cisplatin 항암요법 동시치료시 급성독성 및 초기반응 평가

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목 적:국소적으로 진행된 자궁경부암 환자에서 저용량의 cisplatin을 방사선민감제로 사용하여 방사선치료와 동시치료하였을 때의 급성독성 평가와 초기 반응을 평가하기 위하여 연구를 시행하였다.
대상 및 방법:본 연구는 1996년 12월부터 1999년 1월까지 FIGO Stage IIB-IIIB의 진행된 자궁경부암 환자 38명을 대상으로 하였다. 16명은 자궁경부암의 크기가 4cm이상인 환자들로 방사선 치료와 저용량의 cisplatin을 매일 동시에 치료 하였으며, 나머지 환자에선 방사선 치료 단독으로 치료하였다. 방사선치료는 골반강에 외부 방사선치료로 4500 cGy(3060cGy시행이후 midline block 추가), 자궁옆조직으로 침범이 있는 경우에는 자궁옆조직으로 방사선치료 부위를 줄여 900-1000cGy 추가치료를 시행하였고, 내부치료는 Ir192고선량 근접 치료기(micro-Selectron HDR)로 6-7회의 강내조사(point "A"에 3000 to 3500cGy, 500cGy/fx, 2회/week)를 시행하였다. 방사선치료와 저용량의 cisplatin을 동시에 사용한 군에서는 방사선치료 첫날부터 방사선치료 20일째 되는 날까지 저용량의 cisplatin 10mg을 방사선치료 30분 전에 투여하였다. 급성독성의 평가는 expanded common toxicity criteria of the NCI Clinical Trial을 이용하였다. 초기반응의 평가는 방사선치료 종료이후 최소 4주이상의 추적조사가 가능한 사람들을 대상으로 시행되었다.
결 과:급성독성 평가는 전체 38명에서 평가 가능하였으며, 방사선치료와 저용량의 cisplatin을 병용한 군에서 16명중 6명(37.5%)에서, 방사선 단독으로 치료한 군에서는 22명중 1명(6.2%)에서 3등급 이상의 백혈구감소를 보였으며, 통계학적으로 의미있는 차이를 보였다(P=0.030). 3등급 이상의 급성 위장간독성은 저용량의 cisplatin을 병용한 군에서만 4명이 있었으나, 2-3일의 치료 중단이후 증상이 완화되어서 치료를 계속할 수 있었으며, 치료중 5kg이상의 체중감소는 방사선치료와 저용량의 cisplatin을 병용한 군에서는 16명중 3명(18.7%), 방사선 단독으로 치료한 군에서는 22명중 2명(9.1%)으로 통계학적으로 의미 있는 차이를 보이지 않았다(P=0.63). 초기반응은 추적조사가 4주 이상 가능하였던 34명을 대상으로 하였으며, 저용량의 cisplatin을 병용한 군에서 14명중 11명 (78%), 방사선 단독으로 치료군에서 20명중 16명(80%)으로 통계학적으로는 의미있는 차이를 보이지 않았다(P=0.126).
결 론:국소 진행된 자궁경부암에 대한 방사선치료와 저용량의 cisplatin 병용요법 치료시 3등급 이상의 백혈구감소가 방사선치료 단독으로 치료시보다 많았으나, 1주 이하의 치료중단 이후 치료를 계속 할 수 있었으며, 4등급 이상의 백혈구감소와 치료에 의한 사망은 없었다. 초기반응에 대한 평가는 저용량의 cisplatin병용 군에서 4cm 이상의 자궁경부암을 가진 환자가 많음에도 불구하고 양 군에서 비슷한 정도의 반응을 보였으므로 진행된 자궁경부암의 치료에서 저용량의 cisplatin을 방사선민감제로 사용하여 치료결과의 향상을 기대할 수 있게 되었다. 따라서 저용량의 cisplatin과 방사선치료를 병용요법하였을 때의 치료효과를 판정하기 위해서는 phase III study가 필요하다.

핵심용어:자궁경부암, 방사선민감제, 방사선 항암화학 병용요법