Concurrent Weekly Cisplatin and Radiation Therapy for High risk group of Uterine Cervical Cancer

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Locally advanced cervical carcinoma has shown high rate of local failure and poor survival rate despite the advances in modern radiation therapy techniques. Combination of chemotherapy and radiation therapy demonstrated benefit in improving local control and possibly the overall survival.

Twelve patients with advanced stages (Figo stage III, IV) or 11b with bulky tumors (>5 cm in diameter) were treated with combination of radiation therapy and concurrent weekly cisplatin between May of 1988 and September of 1991 at Inje University Paik Hospital. Cisplatin was administered in bolus injections of 50 mg at weekly intervals during the courses of radiation therapy.

Median follow-up period was 34 months with ranges from 3 to 53 months. Eleven patients were evaluable for the estimation of response. Response was noted in all the 11 patients: complete response (CR) in 7 (64%), partial response (PR) in 4 (36%). Of the 7 patients with CR, all maintained local control, whereas only 1 of 4 with PR showed local control. Six of 7 with CR are alive disease free on the completion of follow-up. Eight of 11 patients (73%) maintained local control in the pelvis. The median survival for CR patient is 27 months and 9 months for the PR patients. Analysis of survival by stage shows 11 b 4/5, III 2/3 and IV 1/3. Overall survival rate was 61%. Three patients recurred: 1 at local, 1 in distant site and 1 with local and distant site.

Toxicity for the combination therapy was not excessive. These results are preliminary, but definitely encouraging in view of markedly improved response rate compared with the results of historical control group.

Key Words: Cervical carcinoma, Concurrent chemotherapy, Cisplatin, Radiation therapy

INTRODUCTION

Effectiveness of radiation therapy reached the maximum for the advanced cervical carcinoma and the local-regional control remains a major problem among oncologists. For stage III and IV, pelvic failure rate reaches up to as much as 50%-70%[1~4]. The combination of radiation therapy and surgery has limited value of improving local control and survival in only barrel-shaped cervices[5]. There emerges a great emphasis on the potential value for chemotherapy[6~14]. Numerous investigations with combination of radiation therapy and chemotherapy are being proceeded to search for the ideal treatment regimen and schedules[15~17]. GOG initiated the experience with cisplatin as a single agent for advanced and recurrent cervical carcinoma and had an overall response rate of 23-40%[8,9]. Subsequent studies also proved the effectiveness of these combined modalities[11~13,15].

In this prospective study, we have evaluated the efficacy and toxicity of concurrent use of radiation therapy and weekly cisplatin in the patients with advanced cervical carcinoma and carcinoma of high risk factors.

MATERIALS AND METHODS

Twelve patients with biopsy-proven advanced carcinoma of the cervix were treated between May of 1988 and September of 1991 in the Department of Radiation Oncology at Inje University Medical College Seoul Paik Hospital.

Their pretreatment characteristics are shown in Table 1. All patients had measurable disease. No patients had previous chemotherapy and none had

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Table 1. Characteristics of Patients

Age; 26-69 yra (median; 54)	
Stage; IIb 5 pts	
III 3 pts	
IVa 4 pts	
Histology; squamous 11 pta	
adeno 1 pt	
Pelvic LN (+) in CT scans; 5 pts	
(hypogastric LN; 3)	

LN; Lymph node,
CT; Computerized tomograph

Table 2. Treatment Protocol

Eligibility of patients	
FIGO Stage III, IV	
IIb with bulky tumor	
Normal BM, hepatic & renal function	
No previous chemotherapy or radiotherapy	
Radiation Therapy	
ERT to whole pelvis,	
5000-6000 cGy/28-34 fraction	
according to stage	
midline block at 4140 cGy	
ICRT	
3000-5000 cGy to point A	
1-2 sessions with 1-2 weeks interval	
Chemotherapy	
Cisplatin 50 mg IV bolus	
on day 1, weekly	
concurrent with radiation therapy	

BM; Bone marrow
ERT; External radiotherapy
ICRT; Intracavitary radiotherapy

Table 3. Evaluation of Patients

Follow-Up Examination
Every one to three months after completion of treatment
Clinical examination
Biochemical profiles
Radiologic tests
Definition of Response
CR; complete disappearance of tumor
PR; regression of $\geq$50% of tumor
SD; regression of $<$50% of tumor
Survival Duration;
From the commencement of radiotherapy
Survival Rate;
Using the Kaplan-Meier method

CR; Complete response, PR; Partial response
SD; Stable disease

received radiotherapy. Initial examination of each patient included history and physical examination and bone marrow, hepatic and renal function tests. Chest X-ray, computed tomograph &/or abdominopelvic sonograph were done to determine the extent of disease.

Median follow-up period was 34 months with ranges from 3 to 53 months. Patients ranged from 26 to 69 years of age (median 54 years). FIGO stage distributions of 12 patients were as follows; IIb, 5: III, 3: IV, 4. Eleven of 12 patients proved to have squamous cell carcinoma. Five patients proved to have suspicious involvement of pelvic lymph nodes with hypogastric being the most frequent site (3/5).

Details of chemotherapy are as follows: Cisplatin 50 mg I.V. bolus injection was given on day 1 and repeated weekly during the course of external irradiation. Prior to each injection of cisplatin, complete blood count and renal function were tested. If the neutrophil count was less than 2000/mm^3 or platelet count was below 75000/mm^3, the drug administration was delayed until it reached the proper level (Table 2). The mean number of chemotherapy courses given was 5 (range 3-7). Eighty three percent of patients completed the entire courses of chemotherapy.

The radiation treatment consisted of external pelvic irradiation with dose ranges from 4980-6480 cGy at 900 cGy per week given in 5 fractions. Median radiation dose was 5160 cGy. Midline structures were shielded from radiation at 4140 cGy. Intracavitary radiation treatment was given in one or two applications with 7-14 days intervals. This delivered radiation dose of 1839-5000 cGy to point A with median dose of 4000 cGy.

Patients were evaluated for the estimation of response every one to three months after the completion of treatment with clinical examination, biochemical profiles and radiologic tests. Complete response (CR) was defined as the disappearance of all clinically detectable tumor for a minimum of 1 month. Partial response (PR) was defined as at least a 50% reduction in the sum of products of the perpendicular diameters of measurable diseases. Stable disease (SD) was defined as less than 50% regression of measurable tumor.

The survival duration and time to relapse were measured from the commencement of radiotherapy. Survival data was obtained utilizing Kaplan-Meier method (Table 3).

RESULTS

Eleven cases were evaluable for the estimation of response. Seven patients (64%) achieved CR and 4 patients (36%) achieved PR with overall response rate of 100%. All 7 CR patients and 1 out of 4 PR patients achieved local control. Of 7 patients with CR, 6 are alive with disease free status on the completion of follow-up. Eight of 11 patients (73%) maintained local control in the pelvis.

The median survival for CR patients is 27 months (range 12-53) and 9 months for PR patients (range 3-12). Analysis of survival rate by stage shows 11b 4/4 (75%), III 2/3 (67%) and IV 1/3 (33%). Overall 5 year survival rate was 61% (Fig. 1). Three patients recurred: one at the primary site, one at the distant site (supraclavicular nodes) and one with both local and distant site (lung).

The major toxicity were nausea and vomiting occured in 3 patients, poor appetite in 4, neutropenia in 4 and thrombocytopenia in 1 patient (Table 4). One patient died from probable sepsis after completion of treatment.

Table 4. Toxicity of Treatment

Toxicity	No. of patients	
Leukopenia		4/12
3000-4000/μl	3/12	
2000-3000/μl	1/12	
1000-2000/μl	-	
Thrombocytopenia		1/12
10-15$\times10^4$/μl	1/12	
5-10$\times10^4$/μl	-	
$<5\times10^4$/μl	-	
Nausea/Vomiting		3/12
Poor appetite		4/12
Nephrotoxicity		-

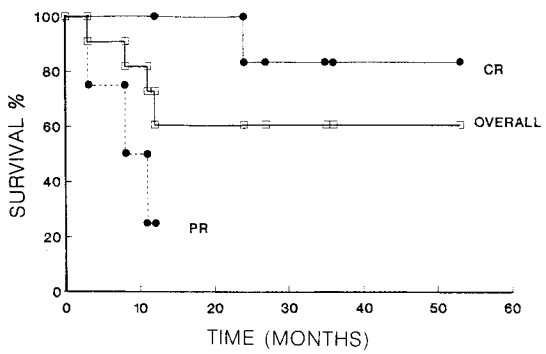

Fig. 1. Survival rate of entire, CR (complete response) and PR (partial response) group.

DISCUSSION

Local control present as a major problem for advanced cervical carcinoma as demonstrated by the high rate of pelvic failure[1~4]. Radiation alone for stage III and IV cervical carcinoma shows 50-70% of pelvic failure rate.

A number of chemotherapeutic drugs have shown significant antitumor activities[6~14]. Cisplatin has been found to be one of the most active agents in cervical caner[8,9,11~13,15]. The feasibility of utilizing cisplatin and radiation therapy was proved by Reimer et al who used cis-platin 20-50 mg/m^2 weekly with irradiation for solid tumors[18] and by Choo et al[15] for stage II and III cervical cancer. We have applied this combined therapy to treat stage III, IV and IIb with bulky tumors which were known to be associated with high local failure rate.

In this study, 7 patients obtained CR (66%) and 4 patients (34%) PR with an overall response rate of 100%. These figures are rather very high compared with radiation therapy alone or chemotherapy alone group which was approximately about 50%[1,4,6~9,12,16,17]. The patients who achieved CR had median duration of survival of 27 months compared with 9 months of PR group. This figure confirms previous findings which showed distinct survival advantages in CR patients[17]. Six of 7 patients with CR remained disease free with median follow-up of 34 months. Local control was obtained in 8 of 11 patients (73%) which was also higher than the historical control group of 30-50%.

The major toxic effects of combined treatment modalities were nausea/vomiting, diarrhea, myelosuppression[11]. Toxicity in our series was not significant and less than the figures of others. Proper symptomatic measurement for toxicities may have reduced the incidence of significant side effects in our study.

In view of the accurual of few patients, it may be hasty to make any conclusions regarding the value of this treatment protocol. But it is encouraging to obtain a rather high overall response rate (100%) with CR rate of 64%.

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국문초록 =

국소적으로 진행된 자궁경부암에 대한 방사선 치료와 Cisplatin의 동시 병행요법의 치료 결과

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국소적으로 진행된 자궁경부암(종괴크기가 5 cm 이상 혹은 FIGO 병기 III, IV) 환자에 있어 방사선 치료 단독으로 근치적치료를 시행한 경우 골반내에서 약 50% 까지의 높은 재발율이 보고되고 있다. 따라서 이들 환자에 있어서 국소관해율 및 생존율을 증가 시키기 위하여 본 연구에서는 방사선 민감제로서 가장 효과적인 약제로 알려진 cisplatin을 방사선치료와 동시에 투여하는 방사선-화학요법을 시행하였다.

1988년 5월부터 1991년 9월까지 인제대학교 부속 서울백병원치료방사선과에서 자궁경부암으로 진단된 환자중 국소적으로 진행된(FIGO 병기 III, IV, 종괴크기가 5 cm 이상의 IIb) 환자로서 방사선치료와 cisplatin의 동시병행요법이 시행되었던 12명을 대상으로 후향적 임상분석을 하였다.

12명의 환자에 대한 치료는 골반부위에 5000 cGy 이상 (4980-6480 cGy)의 외부방사선치료및 1회이상의 강내치료가 시행되었고 동시에 cisplatin 50 mg을 1주 간격으로 반복투여하였다. 총 투여 횟수는 3~7회로 평균 5회였다. 추적기간은 3~53개월(중앙값 34개월)이며, 연령 분포는 26~69세(중앙값 54세)였다. 병기별 분포는 IIb, III, IV가 각각 5, 3, 4명이었다. 조직학적 분류상 편평상피세포암이 11명이었다.

11명의 관찰대상중 완전관해는 7명(64%), 부분관해는 4명(36%)에서 이루어졌다. 7명의 완전관해중 6명이 무병상태였다. 관찰종료시의 전체국소관해율은 73%로서 완전관해군은 100%, 부분관해군은 25% 에서 국소관해를 보였다. 병기별 생존분포를 보면 FIGO 병기 IIb, III, IV에서 각각 4/4, 2/3, 1/3 이었으며 5년생존율은 61% 이었다. 사망자는 4명으로 이중 3명은 일차적인 질병으로, 1명은 패혈증으로 사망하였다. 재발환자는 3명으로 국소재발이 1명, 원격전이가 1명, 국소재발과 원격전이가 1명이었다.

병합치료에 의한 독성을 살펴보면 오심증상이 3명, 식욕부진이 4명, 백혈구감소증이 4명, 그리고 혈소판감소증이 1명에서 관찰되었다. 다른 1명은 치료종료후 패혈증으로 사망하였다. 그 외의 혈액적 독성, 신독성의 증상을 나타낸 경우는 없어 cisplatin 추가에 의한 독성은 경미한 것으로 나타났다.

국소적으로 진행된 자궁경부암 환자에서 방사선-화학요법을 동시병행할 경우 국소관해율이 100%(완전관해율이 64%)이었고 골반내 재발율은 27% 이었으며 cisplatin 추가로 인한 독성은 경미하였다. 이는 대조군과 비교할때 보다 나은 성적으로 예비결과이기는 하나 국소적으로 진행된 자궁경부암 환자에서 방사선치료와 cisplatin 동시병행요법이 국소관해율을 향상시킬 수 있을 것으로 기대된다.