Preliminary Results of Concurrent Radiation Therapy and Chemotherapy in Locally Advanced Cervical Carcinoma

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Since May 1991, authors have conducted a pilot study to determine the feasibility and evaluate the effect of concurrent radiation therapy and chemotherapy with 5-FU and Cis-platinum for locally advanced cervical cancer (stage IIB-IVA).

Radiation therapy consisted of external irradiation to whole pelvis (4140 cGy/23 fx) in 4.5 weeks followed by high dose rate intracavitary radiation therapy (HDR ICRT) to deliver a dose of 30 to 35 Gy to A point in 6 to 7 fractions. After the intracavitary radiation therapy, parametrial boost was delivered for B point dose of 60 Gy in Stage IIB and 65 Gy in stage IIIB. 5-FU (1000 mg/m^2/24hr for 96 hour iv infusion) and Cis-platinum (20 mg/m^2/day IV bolus for 3 days) were given during the second week of external RT and the second course chemotherapy administered at the first HDR ICRT with the same method as the first chemotherapy.

Sixteen patients (10 stage IIB, 4 stage IIIB, 2 stage IVA) were registered to this protocol. Among these 16 patients, two refused treatment after 2 fractions of external irradiation, and one could not continue intracavitary irradiation because of treatment related genitourinary toxicity. So 14 patients were evaluated for toxicity and 13 patients were evaluated for response analysis. Five of 14 patients developed grade 3 gastrointestinal toxicity but 4 of them recovered at the completion of treatment. One stage IIIB patient with inguinal lymph node metastasis who received higher dose of radiation in spite of initial poor performance status did not recover from gastrointestinal toxicity at the completion of treatment. And she died of distant metastasis at one month after the completion of treatment. Two of 14 evaluable patients showed weight loss, more than 10% of initial weight. One patient developed grade 3 leukopenia. In this study, the average total treatment period of completely treated patients was 75 days and three of them took more than 80 days (84, 84, 89 days). Toxicities were generally acceptable and there were no treatment related death. At the last follow-up, complete response was achieved in 62% (8/13) and especially of nine patients with stage IIB, eight patients showed complete response.

This study suggests that concurrent radiation therapy and chemotherapy (5-FU and Cis-platinum) is tolerable and effective. Further follow-up is needed to determine whether this protocol will have a favorable impact on survival and to evaluate the late effect on normal tissues. In future, prospective randomized trials are needed to compare the standard radiation therapy alone with concurrent chemotherapy and radiation therapy for locally advanced cervical carcinoma.

Key Words: Advanced uterine cervical cancer, Concurrent chemotherapy and radiation therapy

INTRODUCTION

While no therapy has been proven more effective than radical external beam plus ICRT, considerable research effort is currently being put into improving pelvic control and survival rates in patients with locally advanced cervical cancer.

An analysis of the pattern of failure after radiation therapy in locally advanced cervical cancer reveals that 72% of those who fail have pelvic tumor as a component of the first site of failure, whereas 63% who develop some component of distant disease have pelvic tumor as their first site of failure[1]. As the bulk of pelvic disease increases, the proportion of patients with disease recurrent or persistent in the pelvis as the only site of failure increases compared to the proportion developing distant metastasis. The problem of enhancing pelvic control can't be approached simply by in-

creasing radiation dose because the late complication produced by conventional radiation alone in locally advanced cervical cancer are at the upper limit of acceptability. Attempts to increase local tumor control have induced use of radiosensitizers such as misonidazole[2], hydroxyurea[3], hyperbaric oxygen[4], and high LET radiation[5]. To date, such methods have demonstrated mimimal improvement in tumor control.

The use of chemotherapy with radiation therapy as a means of improving results in locally advanced cervical cancer evolved. The combination of chemotherapy and radiation therapy is further theoretically appealing in view of in vitro studies that show an increased cell kill in hypoxic environments when the combination, rather than radiation alone, is applied[4]. Concurrent chemotherapy and radiation therapy has been demonstrated to be effective in the local control of advanced squamous cell carcinoma of the anal cancer[6] and potentially may produce improved local control compared to that produced by radiation alone in advanced cervical cancer. A number of chemotherapeutic agents appear to have modest activity in metastatic or recurrent cervical cancer. The chemotherapeutic agents used in this stady, Cis-platinum and 5-FU, have the theoretical dual advantages of radiation effect enhancement and direct cytotoxity[7,8]. When they are combined with radiation therapy in optimal time and dosage, the gain is to increase local control and decrease distant metastasis, leading to an improvement in survival rates. In this study, Cis-platinum and 5-FU were given concurrently with radiation therapy to address the potential of tumor cells to repopulate if the two modalities were used sequentially. The time dose delivery mechanisms used in the protocol were based on specific available radiobiological data[9]. Unfortauately, the potential of enhancing normal tissue toxicity also exists when these agents are combined.

This study was designed to determine the feasibility and toxicity of concurrent radiation therapy and chemotherapy with 5-FU and Cis-platinum and to estimate the local control rate for locally advanced cervical cancer patients. This is a preliminary report on its outcome with particular emphasis on toxicity.

MATERIALS AND METHODS

1. Patients Selection

Patients with biopsy-proven squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the cervix, FIGO Stages IIB, IIIA, IIIB and IVA were eligible. Karnofsky performance status of $>60\%$ and age of $\leqq 70$ were required. The patient had no history of prior chemotherapy, radiotherapy, or surgery for cancer. Adequate hematological, renal, and hepatic function were required. All patients were required to sign an informed consent. Patients with lymphadenopathy outside the pelvis were ineligible as were patients with metastatic disease.

2. Pretreatment Evaluation

All patients underwent complete history and physical examination and had histological proof of cervical carcinoma. Fraction curettage with endometrial curettings was recommended whenever feasible. A complete blood count, liver and renal chemistries, a chest X-ray, and a computerized axial tomogram (CAT scan) with contrast or MRI of the abdomen and pelvis were mandatory. Cystoscopy, sigmodoscopy, barium enema, and metastatic evaluation by radioisotopic scans were to be obtained at the discretion of the individual investigator.

3. Protocol Treatment

Patients received 4140 cGy to the whole pelvis in 4.5 weeks. 5-FU (1000 mg/m^2/24hr) was administered by a 96 hour infusion along with Cis-platinum (20 mg/m^2/day IV bolus for 3 days) during the second week of external radiation therapy. After external irradiation to whole pelvis, the patient then received 6 or 7 high dose rate intracavitary radiation therapy (HDR ICRT) to delivery 500 cGy to A point each time followed by a 900~1000 cGy boost to the parametrium. The second course chemotherapy was administered at first HDR ICRT. Total treatment time was 70 ± 7 days.

4. Study Parameters and Follow-Up

The major study endpoints were toxicity and pelvic disease clearance. The ECOG toxicity criteria were used for hematological and other toxicity. Patients were assessed at completion of second chemotherapy for toxicity and assessed at completion of treatment and subsequent one month intervals for disease clearance. Complete response was defined as the complete disappearance of all visible and palpable disease and partial response was defined as 50% or greater reduction of all visible and palpable disease.

RESULTS

Between May 1991 and August 1993, twenty five patients with FIGO stages IIB, IIIA, IIIB and IVA were evaluated for inclusion into the study in our department. Of these 25 patients, only sixteen patients were eligible for the protocol and nine patients were ineligible since two patients received prior chemotherapy, two patients had poor renal function and five patients refused combined treatment. The characteristics for eligible and ineligible patients are summarized in Table 1.

There was no difference in characteristics between these two groups. Sixteen patients were registered to this study. Patients were analyzed separately for toxicity and tumor response (Table 2). Two patients were ineligible for both analyses since they received only 2 fractions of external irradiation, 360 cGy. Another one patient was not evaluable for response analysis since this patient interrupted intracavitary irradiation because of grade 3 genitourinary toxicity.

Most common nonhematologic toxicities were nausea and vomiting probably secondary to Cisplatinum, and diarrhea secondary to a combined effect of 5-FU and radiation therapy. At the time of completion of second course of chemotherapy, five of 14 patients had grade 3 gastrointestinal toxicity and none had grade 4 toxicity. Four of five patients with grade 3 gatrointestinal toxicity recovered completely at the completion of treatment, but one patient did not recover. This patient with stage IIIB and inguinal lymph node metastasis received higher dose of radiation in spite of initial poor performance status and died of lung metastasis at one month after treatment. One patient developed grade 3 genitourinary toxicity after second course of chemotherapy and could not complete intracavitary radiation. Two of 14 evaluable patients showed weight loss, more than 10% of initial weight.

Hematologic toxicities are discribed in Table 3. Only one patient developed grade 3 leukopenia. Despite this myelotoxicity, there was no treatment delay or septicemia.

According to this protocol treatment, duration of treatment is about 70 ± 7 days. In this study, the average duration of treatment was 75 days and 3 patients took more than 80 days (84, 84, 89 days). A review of the reasons for these treatment delay revealed that all patients were due to grade 3 gastrointestinal toxicity.

Responses were evaluated in 13 patients at the completion of radiation therapy and the last follow-up (Table 4). No progression of disease was observed during treatment. At the completion of radiation therapy, complete response (CR) and partial response (PR) rates were 38.5% (5/13) and 62% (8/13) respectively. In patients with stage IIB, CR and PR were achieved in 5/9 and 4/9 respectively. At the last follow-up, CR and PR were achieved in 8/13 and 3/13 respectively. Of 4 patients with stage IIB who showed PR at the completion of treatment, three showed complete

Table 1. Characteristics of Patients at Study Entry

	Eligible Patients	Ineligible Patients	Total
No. of Patients	16	9	25
Age in years range	40~77	51~76	40~76
≦49	2	0	2
50~59	7	2	9
60~69	6	3	9
≧70	1	4	5
Karnofsky P.S.			
60~70	2	2	4
80~90	3	3	6
90~100	11	4	15
FIGO Stage			
IIB	10	4	14
IIIB	4	4	8
IVA	2	1	3

remission at the last follow-up. One patient with stage IIIB with inguinal lymph node metastasis and one with stage IVA died of systemic metastasis at 1 month and 3 months after completion of treatment. These patients had poor performance status initially.

DISCUSSION

The use of chemotherapy with radiation therapy as a mean of improving results in advanced cervical cancer evolved as a results of (a) disheartening results from studies using the radiosensitizer misonidazole, hydroxyurea, and hyperbaric oxygen[3,4] with radiation therapy and neutron beam therapy[2,5], (b) the virtually static survival rates in the last 3 decades despite the establishment of the megavoltage era in radiation therapy[10]. (c) encouraging results in certain epithelial (head and neck, anal) cancer[8,11] treated with the empirical combination of some drugs with radiation therapy[12,13], and (d) a growing awareness that metastatic extrapelvic failure was important component of overall failure. Thus, this concurrent chemotherapy and radiation therapy was directed toward improving local control as well as reducing distant metastasis.

A variety of single agents or combination of cytotoxic drugs have been evaluated in small group of patients with advanced metastatic or recurrent carcinoma of cervix. Initially, in the chemotherapy agents 5-FU and Cis-platinum were chosen on the basis of radiobiological and clinical data on their use with concurrent radiation in the management of advanced cervical cancer (Table 5)[9,14~17]. Radiosensitizing properties of 5-FU and Cis-platinum have been amply demonstrated in the experimental setting and clinical trials have shown possible radiosensitization[18~22]. Cis-platinum has a 38%

Table 2. Evaluability Status

Evaluability Status	For Response Analysis	For Toxicity Analysis
Registered	16	16
Refused further Tx	3*	2
Evaluable	13	14

*Two patients received external irradiation of only 2 fractions and another one patient received external irradiation and 2 cycles of chemotherapy.

Table 3. Hematologic Toxicity in 14 Evaluable Patients

WBC count	Grade	No. of Patients
3000~4400	1	12
2000~2900	2	1
1000~1900	3	1
>1000	4	0

Table 4. Response Rates in 13 Evaluable Patients

Stage	No. of patients	At Completion of Tx		Last Follow Up*	
		PR	CR	PR	CR
IIB	9	4	5	1	8
IIIB	2	2	0	1	0
IVA	2	2	0	1	0
Total	13	8	5	3	8

CR: Complete Response, PR: Partial Response.

*Two patients (stage IIIB, IVA) died of systemic metastasis at 1 month and 3 months after completion of treatment.

Table 5. Studies of Concurrent Chemotherapy and Radiation Therapy

Author (reference)	No. of patients	Drugs	CR (CT+RT)
John (9)	38	PFM	62.5%
Souhaml (14)	31	P	78%
Robert (15)	21	PF	86%
Mickiewicz (16)	18	MFP	83%
Malviya (17)	19	PM	95%
This Study	13	PF	62%

response rate in metastatic cervical cancer[23]. Cis-platinum has relatively little bone marrow toxicity to potentially interfere with the administration of radiation therapy. In vitro data suggested that the addition of infusional 5-FU to radiation therapy would enhance the radiation effect[21]. The underlying mechanism is not defined and is unknown whether additive results from simple independent additivity or from an interaction of the two modalities. In the data of Byfield et al. the increased cell kill appeared to depend on the period of exposure to 5-FU and was greatest if the drug was present for intervals in excess of 48 hours after radiation was performed. Nakajima et al. had shown that enhanement could be improved by increasing the concentration of 5-FU[22]. But the optimal clinical method for combining 5-FU and radiation to exploit drug-radiation interaction remains undefined. The concept of concurrent radiation and chemotherapy offers a number of theoretical advantages compared to the use of neoadjuvant chemotherapy. Concurrent therapy produces no delay in the start of definitive irradiation. The entire treatment course is not prolonged and the effects of tumor proliferation are therefore minimized. The potential interaction of concurrent chemotherapy, particularly in the form of 5-FU or Cis-platinum, with radiation treatment may lead to increased tumor cell kill. The chemotherapeutic agents may exert an independent cytotoxic effect on the primary tumor, particularly if they affect a target population different from that affected by the radiation therapy. While the combination of concurrent radiation and chemotherapy offers potential advantages for tumor cell kill, some theroretical disadvantages also exist for this combination. First, addition of chemotherapeutic agents to radiation may increase the acute toxicity exhibited by normal tissues and thus could limit the dose of definitive radiation employed. This was particularly important with respect to the use of 5-FU, as one of its major toxic effects in damage to the bowel mucosa and the acute dose limiting effect of pelvic irradiation similarly is the tolerance of bowel. Second, if the addition of chemotherapecutic agent leads to increase late toxicity, i.e., increased effect on normal tissues, then the therapeutic ratio would be unfavorable. The last disadvantage of concurrent therapy is that one or two doses of systemic agents are unlikely to influence established micrometastases or prevent disease dissmination. The time dose delivery mechanism used in the protocol were based on specific available radiobiological data and theoretical advantage and disadvantage.

Acute tolerance was defined by weight loss, treatment delay, hematologic, gastrointestinal toxicity. Although grade 3 gastrointestinal toxicity has developed in 5/14, four of them recovered at completion of treatment. Patients with 10% reduction of pretreatment weight was 2/14 and patients with more than 10 days delay was 1/13. Grade 3 hematologic toxicity was developed in 1 patient. Current study demonstrated good acute tolerance to concurrent chemotherapy and radiation therapy, even though most patients developed anorexia, nausea, fatigue and malaise on the day of administration of chemotherapy.

We can not draw any conclusion in this study as yet because of the small number of patients, variability in the patient population with regard to extent of disease, and short follow up period. But we are encouraged by the observation that all patients with stage IIB responded to treatment, with CR rate of 89% (8/9). However, no patients with stage IIIB and IVA showed CR and two of them died of systemic metastasis. Thus, the modification of treatment for improvement of local control and prevention of systemic metastasis must be considered in patients with stage III and IVA since this prorocol showed acceptable tolerance. First, authors consider to shorten the total treatment time within 5 to 6 weeks. To reduce the total treatment time, hyperfractionated irradiation or combined external radiation therapy with HDR ICRT may be considered. The purpose of hyperfractionated irradiation is three fold. The first purpose is to deliver a higher total dose of radiation during the 5-FU infusion and allow for more prolonged exposure to 5-FU following a total higher radiation dose. According to Byfield et al[21], this may lead to increased cell kill if 5-FU and radiation interact. The second purpose was to exploit a therapeutic advantage for the use of smaller doses per fraction. Radiobiological data suggest that the late toxicity of radiation may be decreased by decreasing the dose per fraction of radiation[24], thus the decrease in fraction size was made particularly important when two treatments per day were given. Third, radiobiologic data suggest that prolonging a course of radiation treatment beyond about 4 weeks may be associated with accelerated tumor clonogenic cell proliferation. Second, authors consider optimization of radiation therapy and chemotherapy sheduling and dosage to improve local control and to decreas distant metastasis, leading to improvement in survial rates.

In summary, a combination of concurrent radiation and chemotherapy in patients with locally advanced cervical carcinoma was accomplshed with acceptable toxicity. Longer follow-up of our patients is needed to determine whether this regimen will have a favorable impact on survival and to assess the late effect on normal tissue. Randomized trials are needed to compare the standard radiation therapy alone with concurrent chemotherapy and radiation therapy for locally advanced cervical cancer.

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= 국문초록 =

국소적으로 진행된 자궁 경부암에서 방사선과 항암화학요법 병행치료의 예비적 결과

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양광모 · 안승도 · 최은경 · 장혜숙 · 김영탁* · 남주현* · 목정은*

본 연구는 1991년 5월부터 국소적으로 진행된 자궁경부암(FIGO stage IIB~IVA) 환자를 대상으로 5-FU와 Cis-platinum을 방사선 치료와 동시에 투여하여 치료 독성, 치료의 적합성과 국소관해율을 평가하기 위해 시행되었다.

방사선 치료는 외부방사선 조사로 전골반부에 23회에 걸쳐 4140 cGy 시행후, 고선량 근접치료기로 강내조사를 6회 내지 7회(A점에 3000~3500 cGy) 시행하였으며, B점에 추가조사를 시행하여 IIB 병기 환자는 6000 cGy까지 IIIB 병기 환자는 6500 cGy가지 B점에 조사되도록 하였다. 첫번째 항암화학요법은 외부방사선 치료 시행의 두번째 주에 5-FU는 1000 mg/m²/24hr를 96시간 동안에 걸쳐 토여하고 Cis-platinum은 20 mg/m²/day를 3일 투여하였다. 두번째 항암화학요법은 처음과 동일한 방법으로 첫번째 고선량 근접 강내 치료가 시행될 때 투여 되었다.

1993년 8월까지 총 16명의 환자(10 IIB 병기, 4 IIIB 병기, 2 IVA 병기)가 등록되었으며, 이중 2명은 외부방사선 2회 조사후 치료를 중단하였으며, 1명은 강내치료중 3등급의 비뇨기계독성으로 치료를 중단하였다. 2회의 항암화학 요법이 종료된 후 독성의 평가가 가능했던 14명의 환자중 5명이 3등급의 위장관 독성이 발생하였으나, 4명은 치료 종료 후 평가에서 회복 되었다. 1명은 병기 IIIB 환자로 초기에 서혜부 임파절 전이가 있어 다량의 방사선이 조사되었는데, 치료종료 후에 위장관독성이 악화되었고, 1개월후 원격전이로 사망하였다. 치료후 치료전 체중의 10% 이상 감소된 환자는 2명이었고, 1명이 3등급의 백혈구 감소를 보였다. 환자의 평균 치료 기간은 75일(표준 치료 기간은 70±7일)이었고, 80일 이상인 환자는 3명(84, 84, 89일)이었다.

추적관찰 가능했던 13명 환자중 8명이 완전관해를 보였고, 특히 IIB 병기 환자의 경우 9명중 8명이 완전관해를 보였다.

본 연구결과 진전된 자궁 경부암에서 방사선과 항암화학요법 병행치료는 효과나 독성면에서 수용가능 하였으나 향후 근치적 방사선치료 단독으로 시행된 경우와의 전향적 비교연구가 필요할 것으로 생각된다.