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Concurrent Chemotherapy and Radiotherapy in Invasive Cervical Cancer Patients with High Risk Factors

The aim of this study was to evaluate the survival of 395 previously untreated cervical cancer patients with at least one high risk factor following concurrent chemoradiation and to assess the toxicities. Two different chemotherapy regimens were used for concurrent chemoradiation. In the patients with squamous cell carcinoma, 100 mg/m^2 of cisplatin was infused intravenously, followed immediately by five consecutive daily administrations of 5-fluorouracil, 1,000 mg/m^2/day, each infused intravenously over 24 hr. As for the patients with adenocarcinoma, 70 mg/m^2 of cisplatin, 250 mg/m^2 of cytoxan and 45 mg/m^2 of adriamycin were administered intravenously on days 1, 2, and 3, respectively. The 5-year survival rate was 54.4% with stage III and IV, 62.6% with lymph node metastasis on computed tomogram or MRI, 77.9% with stage I-II disease with lesion size $\geq$4 cm, and 50.3% with small cell carcinoma or adenocarcinoma. Side effects from concurrent chemoradiation such as nausea, vomiting, and alopecia were present in all 395 cases. Anemia, leukopenia, thrombocytopenia, hepatotoxicity, and nephrotoxicity were observed to varying degrees, but there was no toxic death. This study suggests that cisplatin-based concurrent chemoradiation in treating cervical cancer patients with high risk factors is effective and relatively well tolerated, with acceptable toxicity.

Key Words: *Concurrent Chemoradiation; Cervix Neoplasms; Risk Factors; Radiation*

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INTRODUCTION

It is generally accepted that radiotherapy and surgery are both effective techniques in the management of carcinoma of the cervix with small lesions. However, disease control for groups with high risk factors (HRF) such as advanced stage (1), bulky disease (2, 3), lymph node metastasis (2, 3), or small-cell carcinoma (4) is difficult even with the use of modern megavoltage equipment and optimal fractional schemes or improved extensive surgery. The high treatment failure rate and poor survival with conventional treatment have spurred the development of new treatment modalities. With the advent of newer chemotherapeutic agents, chemotherapy has emerged as an additional mode of therapy in these patients. As a result, many investigators have studied the combined modalities of chemotherapy and radiotherapy. It has been hypothesized that chemical debulking attained with cytotoxic drugs may induce better oxygenation of previously hypoxic tumor cells, thereby facilitating response to concurrent radiation and perhaps the control of micrometastasis (5). Numerous reports of locally advanced cervical cancer comparing the concurrent and sequential combination of chemotherapy and radiotherapy have been published with conflicting outcomes. Although some studies have shown promising results with the use of radiotherapy in combination with sequential chemotherapy in advanced disease (6-8), there have also been some negative reports (9-11). Although several studies have documented 90% response rates using radiotherapy with concurrent chemotherapy in poor prognostic cervical cancer patients, there have also been some negative reports indicating that there was no demonstrable benefit of concurrent chemoradiation compared to conventional radiotherapy (12, 13). Roberts et al. (14) reported a clinical complete response (CR) rate of 85% among 67 cases of advanced disease treated in this manner. However, survival did not improve due to local recurrence.

The theoretical advantages of concurrent chemoradiation are the absence of delay in the administration of radiation, shorter treatment duration, and possible enhanced tumor control due to potential synergistic effects. However there is the theoretical disadvantage that concurrent chemotherapy will cause more severe toxicity than radiotherapy alone (15).

This study was aimed at evaluating concurrent cis-

platin-based chemotherapy and radiotherapy in prolonging patient survival in invasive cervical cancer with one or more of the several HRFs. The validity of these prognostic factors was supported by our own retrospective survival analysis of invasive cervical carcinoma cases treated with radiotherapy alone at our institute (1). The toxicities of concurrent chemoradiation were also evaluated.

MATERIALS AND METHODS

The three hundred and eighty-six cases of invasive cervical carcinoma treated with radiotherapy alone at Yonsei University Medical Center (YUMC) from 1976-1984 were statistically analyzed to delineate the high risk factors associated with a significantly high treatment failure rate. These HRF included: 1) stage III-IV disease, 2) lymph node metastasis on computed tomogram or MRI, 3) stage I-II when the primary lesion size $\geq$4 cm, 4) small cell carcinoma or adenocarcinoma (2).

Between 1984 and February 1997, a total of 395 patients with at least one of these HRF underwent clinical trial with concurrent chemoradiation and were followed at YUMC. The clinical staging of these patients was done according to the FIGO classification. For staging, baseline studies included the physical examination, chest radiography, intravenous pyelography, and pelvic computed tomogram or MRI. Pelvic computed tomogram or MRI was employed primarily to evaluate the presence of lymph node enlargements and replace procedures like cystoscopy and sigmoidoscopy. Cystoscopy and sigmoidoscopy were performed in appropriate cases. The mean age of these patients was 52 yr (range, 28 to 74 yr). All concurrent chemoradiation candidates received no prior chemotherapy or radiotherapy. Each patient received 1 to 6 cycles (mean, 3.42 cycles) of concurrent chemoradiation, at approximately 3 weeks intervals, establishing a total of 1,351 cycles.

Two different chemotherapy regimens were used for concurrent chemoradiation. For squamous cell carcinoma, cisplatin 100 mg/m^2 or carboplatin 400 mg/m^2 was infused intravenously and was followed immediately by five consecutive daily doses of 5-fluorouracil 1,000 mg/m^2/day, each as a 24-hr intravenous infusion. For adenocarcinoma, 70mg/m^2 of cisplatin or carboplatin 350 mg/m^2, 250 mg/m^2 of cytoxan and 45 mg/m^2 of adriamycin were administered intravenously on days 1, 2, and 3, respectively.

All patients received the same dosage of radiation in the same manner regardless of therapy regimen employed. External pelvic irradiation was delivered using a 10 MV linear accelerator in daily fraction of 1.8 Gy, 5 days a week. The dose to the whole pelvis was 45 Gy for 5 weeks. Parametrial boost radiation was given for 1-1.5 weeks with a dosage of 10-15 Gy. Remote afterloading intracavitary radiation using high-dose-rate Co-60 sources was given with the total dose of 39 Gy to point A for 3.5 weeks with a fraction size of 3 Gy. Total elapsed time did not exceed 10 weeks. Second courses of chemotherapy were delivered during intracavitary radiation.

The response to concurrent chemotherapy and radiotherapy was assessed after completion of radiotherapy. CR was determined by a complete disappearance of all measurable lesions for at least 1 mo. Partial response (PR) was a more than 50% reduction in lesion diameter with no demonstrable disease progression elsewhere. Stable disease (SD) was a less than 50% decrease or 25% increase in lesion diameter without the appearance of a new lesion. Progressive disease was a more than 25% increase in lesion diameter with or without the appearance of a new lesion. Those patients showing CR or PR to concurrent chemoradiation were considered as responders.

Hematologic, renal, hepatic, cardiac, and lung functions were apparently normal in all 395 patients prior to concurrent chemoradiation. The 24-hr urine creatinine clearance was measured before each cycle was initiated; a minimum of 50 mL/min was considered eligible for chemotherapy. Complete blood count, SMA-12, and serum electrolytes were monitored daily before and during each chemotherapy cycle. Serum hemoglobin was maintained above 12 g/mL. Audiometry and neurologic examination were performed in the presence of suspicious oto- or neurotoxicity.

"GOG common toxicity criteria grade (October 1988)" was used for toxicity grading, and toxicity frequency was assessed in each chemotherapy cycle. Several different toxicities occurring in a given patient, including each chemotherapy cycle, all contributed to the overall toxicity data. Depending on the severity and duration of toxicity, the drug dosage was reduced, or the ongoing drug schedule was delayed or stopped.

The "life-table method" was used to obtain the 5-year survival rate after concurrent chemoradiation.

RESULTS

Patient characteristics

The patients with stage III-IV included 25 cases (6.3%); with lesion size $\geq$4 cm in stage I-II, 14 cases (79.9%); with lymph node metastasis on computed tomogram or MRI, 97 cases (24.6%); with small cell carcinoma or adenocarcinoma, 43 cases (10.9%) (Table 1).

Table 1. Patient characteristics

High risk factors	No. of patients	%
Stage III-IV	25	6.3
Lesion size ≥4.0 cm in stage I-II	314	79.9
Lymph node metastasis*	97	24.6
Small cell carcinoma or adenocarcinoma	43	10.9

*on computed tomogram or MRI

Table 2. Response to concurrent chemoradiation in 395 patients

Response	Frequency	%
Complete response	248	62.8
Partial response	118	29.9
Stable disease	16	4.1
Progressive disease	14	3.3

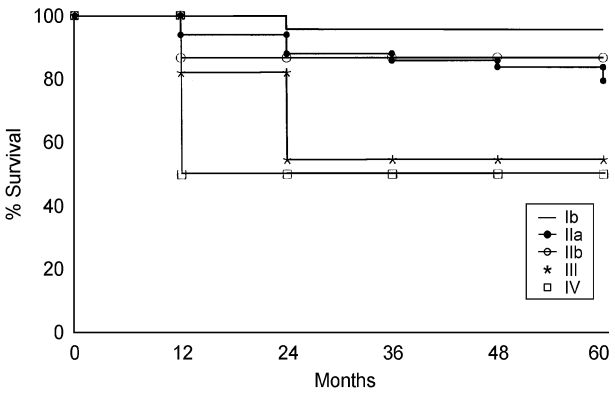

Fig. 1. Survival of patients according to stage.

Response to concurrent chemoradiation

The overall response rate to concurrent chemoradiation was 92.7%; CR and PR rates were 62.8% and 29.9%, respectively. There were 30 non-responders (16 SDs and 14 PDs) (Table 2).

The 5-year survival of patients treated with concurrent chemoradiation

The 5-year survival of patients with stage III and IV was 54.4% (Fig. 1); stage I-II with lesion size more than 4cm, 77.9% (Fig. 2); lymph node metastasis on computed tomogram or MRI, 62.6% (Fig. 3); and small cell carcinoma or adenocarcinoma, 50.3% (Fig. 4).

Toxicity of concurrent chemoradiation

Three hundred and ninety-five patients received concurrent chemoradiation totaling 1,351 cycles. The details of the toxicities are summarized in Table 3. Nausea, vomiting, and alopecia, although varied in degree, were present in all 1,351 cycles. The most common hematologic toxicities were granulocytopenia (43.9%), leukopenia (42.8%), anemia (29.2%), and thrombocytopenia (23.3%). The incidence of hepatic and renal toxicity was 21.6% and 8.8%, respectively. Other acute toxicities

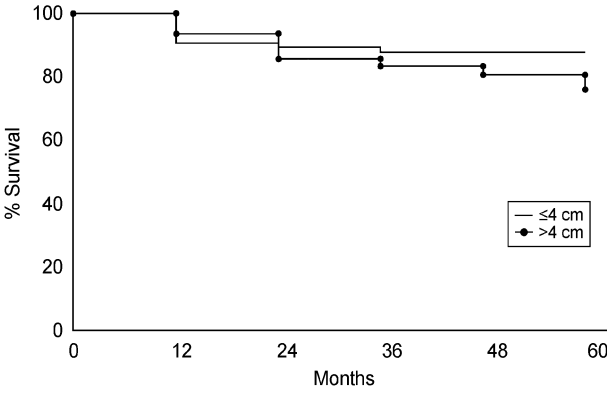

Fig. 2. Survival of patients with stage I-II according to lesion size.

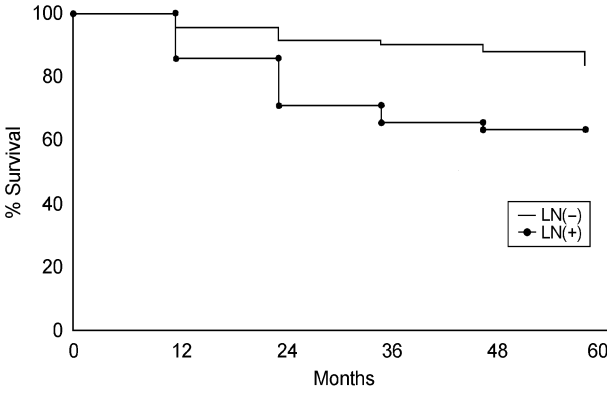

Fig. 3. Survival of patients according to lymph node metastasis on CT or MRI.

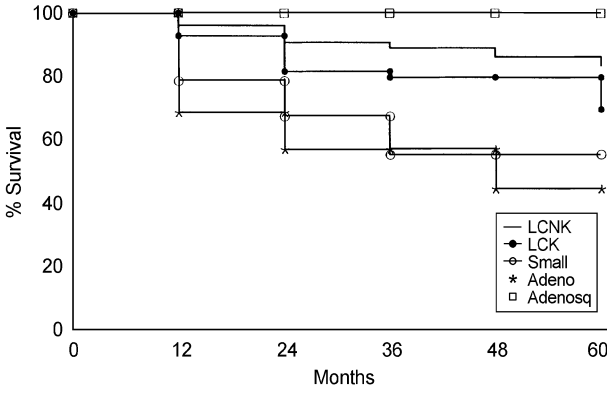

Fig. 4. Survival of patients according to cell type.

Table 3. Toxicity of concurrent chemoradiation

Toxicity	Toxicity grade*				
	1 No. †(%)	2 No. (%)	3 No. (%)	4 No. (%)	Total No. (%)
Hb	322 (23.8)	65 (4.8)	7 (0.6)	0 (0)	394 (29.2)
WBC	360 (26.6)	113 (8.4)	58 (4.3)	48 (3.5)	579 (42.9)
Granulocyte	298 (22.0)	144 (10.6)	106 (7.8)	48 (3.5)	596 (43.9)
Platelet	120 (8.9)	75 (5.6)	34 (2.5)	86 (6.3)	315 (23.3)
AST/ALT	192 (14.2)	82 (6.1)	17 (1.3)	0 (0)	291 (21.6)
CCr	113 (8.2)	4 (0.3)	0 (0)	0 (0)	117 (8.7)
BUN/Cr	1 (0.07)	0 (0)	0 (0)	0 (0)	1 (0.07)

*According to "GOG common toxicity grade - October 1988"
†Number of chemotherapy cycles

Table 4. Modification of concurrent chemoradiation schedule*

Schedule	Frequency	%
Delayed	270/1,351	20.1
Stopped	218/1,351	16.2
Dose reduced	128/1,351	9.5

*based on toxicities

included a case of radiation enteritis and a case of cerebellar dysfunction caused by 5-fluorouracil. No toxic deaths occurred. With regard to the toxicity of concurrent chemoradiation, 20.1% of the therapeutic schedule was delayed, 16.2% of therapeutic schedule was suspended, and 9.5% of the therapeutic schedule dosage of chemotherapeutic agents was reduced (Table 4).

DISCUSSION

Treatment failure can be the result of progressive metastatic disease outside the pelvis but in 70% of treatment failures there is persistent or recurrent disease within the treated volume in the pelvis (16). Approximately 30% of patients die from uncontrolled local disease with no evidence of metastatic disease (17). The thrust of clinical research in advanced cervical carcinoma has been directed toward increasing local control – hypoxic radiosensitizers (18, 19), hyperbaric oxygen (20), radioprotector (21), neutron therapy (22), hyperthermia (23, 24), and hyperfractionation (25) – but most have shown little or no success. The reasonably achievable approach of enhancing the effect of radiation for advanced cervical cancer is combined chemoradiation. The combination of chemotherapy and radiotherapy can decrease distant metastasis and yield a synergistic effect with radiotherapy and local primary tumor control (6, 26).

Sequential chemotherapy was used previously as a modality of treatment, but there were some critical reports on this method. Withers et al. (10) suggested that chemotherapy, which is effective in killing cells, could also lead to accelerated regrowth of surviving clonogens, reducing the effect of subsequent radiotherapy. Thus, Souhami et al. (11) suggested that the use of concomitant chemotherapy and radiotherapy may prove useful in circumventing the problem of accelerated regrowth of surviving clonogens.

Cummings (27) reported a 90% local control rate in squamous cell carcinoma of the anal canal with concurrent chemotherapy. Subsequently, the same method was used in cervical cancer. Thomas et al. (28) reported that radiotherapy with concurrent chemotherapy showed a better local control rate in recurrent carcinoma of the cervix than radiotherapy alone. Malviya et al. (29) reported a 95% cure rate in 19 poor prognostic cervical cancer patients with little toxicity. Morris et al. (30) reported 73% 5-year survival rate in advanced cervical cancer patients treated with radiotherapy and concurrent chemotherapy. Following these reports, radiotherapy with concurrent chemotherapy used in advanced cervical cancer of large tumor volumes has resulted in a high CR rate and a higher survival rate. Therefore this method is recommended as an effective treatment mode for poor prognostic cervical cancer (29-34). The principal rationale of radiotherapy with concurrent chemotherapy regimens is that the adjuvant chemotherapy has a more than additive effect when combined with radiotherapy, resulting in a synergic anti-tumor effect. Also, radiotherapy can be delivered immediately, resulting in a shorter total treatment period; therefore, it is a more economic treatment modality. On the other hand, the combination of chemotherapy and radiotherapy in a concurrent manner can produce severe synergistic toxic effects on normal tissue. This toxicity can restrict the therapeutic dose and schedule, resulting in a less effective treatment. Roberts et al. (14) also reported a high clinical chemotherapy rate (85%), but the survival rate did not increase due to recurrence from local treatment failure. Drescher et al. (13) reported that there was no demonstrable beneficial

effect of continuous infusion of low dose 5-fluorouracil chemotherapy concurrent with radiation therapy compared to conventional radiotherapy in patients with advanced squamous cell carcinoma of the cervix.

Up to the present, most of the literature (29-35) has suggested that radiotherapy with concurrent chemotherapy has minimal toxicity and does not usually delay treatment. Our findings show that treatment schedule was delayed in 270 of 1,351 cycles (20.1%) and stopped in 218 of 1,351 cycles (16.2%). The cause of treatment interruption in approximately 88% of cycles was hematologic toxicity. The bone marrow toxicities of more than moderate degree were seen more frequently than toxicities of other organs – granulocytopenia was seen in 21.9% of patients, leukopenia in 16.2%, thrombocytopenia in 14.4%, and anemia in 5.4%. There were no toxic deaths. There are some differences in toxicity data among various researchers (32, 36), but this is thought to be due to different drug regimens and dosages. Therefore, careful selection of treatment regimens and RT techniques should result in a higher success rate of treatment with minimal toxicity.

In this study, the overall response rate to concurrent chemoradiation was 92.7% (CR: 62.8%, PR: 29.9%). The response rate was higher than the results of Tseng et al. (90%) (11) or Kersh et al. (88%) (12). In cases of stage III-IV disease, the 5-year survival rate was 54.4%. Generally, the 5-year survival rates of patients with stage III-IV disease have been reported as 34-55% (1, 2). In cases of stage I-II with lesion size $\geq$4 cm, the 5-year survival rate was 77.9%. In cases of lymph node metastasis on computed tomogram or MRI, the 5-year survival rate was 62.6% while 5-year survival of patients with lymph node metastasis has been previously reported as 30-50% (37, 38). The 5-year survival of small cell carcinoma or adenocarcinoma was 50.3%. The results will require more careful verification via randomized prospective study, but we can suggest that concurrent chemoradiation may be effective for cases with bulky primary disease and may improve patient survival.

This study suggests that cisplatin-based concurrent chemoradiation in treating cervical cancer patients with high risk factors is effective and relatively well tolerated, with acceptable toxicity. Concurrent chemotherapy and radiotherapy resulted in improved 5-year survival rates in both stage I-II cases with lesion size $\geq$4 cm and also in cases with lymph node metastasis on computed tomogram or MRI.

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