



## Concomitant chemo-radiation in locally advanced carcinoma of the cervix

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**OBJECTIVE(S) :** To determine whether concurrent chemo-radiotherapy with cisplatin and gemcitabine can change the poor outcome in locally advanced cervical carcinoma.

**METHOD(S) :** Eight hundred sixty-seven previously untreated patients with locally advanced cervical carcinoma (FIGO stage II B to IVA) were eligible to enter the study. They were intended to receive external beam radiotherapy and concomitant weekly chemotherapy with cisplatin and gemcitabine to be followed by intracavitary brachytherapy.

**RESULTS :** Sixty-seven patients included in the study had withdrawn themselves mainly due to diarrhea, which was the most common nonhematological toxicity. Anemia and leukopenia were the most important hematological toxicities. Complete local control rate was 67 % at 3 months after completion of treatment, which was subsequently reduced to 60 % at a median follow up of 10.5 months.

**CONCLUSION(S) :** Concurrent chemo-radiotherapy with cisplatin and gemcitabine has shown promising result in locally advanced cervical carcinoma that otherwise has a dismal prognosis.

**Key words :** locally advanced cervical carcinoma, concurrent chemo-radiotherapy, cisplatin gemcitabine

### Introduction

Carcinoma of the uterine cervix is the third most common malignant disease affecting women worldwide, and the number of patients diagnosed with and dying of cervical cancer were estimated to be 4,70,606 and 2,33,372 respectively in the year 2000<sup>1</sup>. However reported incidences and mortality rates for cervical cancer show wide geographic variation and approximately 80 % of all cervical cancer cases occur in developing countries. In the department of radiotherapy of Nil Ratan Sircar Medical College and Hospital, Kolkata, it constituted 32 % of all female cancer patients

attending our radiotherapy department in the year 2004.

In the last 50 years, primarily because of health consciousness and introduction of screening with Pap smear, incidence and mortality rate for invasive cervical cancer have declined significantly in developed countries<sup>2</sup>. But in developing countries like India, even today, most patients present at a locally advanced stage (FIGO IIB – IVA).

A combination of external beam radiotherapy (EBRT) and intracavity brachytherapy (ICRT) is the treatment of choice in advanced stage carcinoma cervix. Barillot and colleagues<sup>3</sup> reported 5 year survival rates of 70%, 45% and 10% in patients with stage IIB, IIIB and IVA tumors respectively, when treated with radiotherapy according to Fletcher's guidelines, and these figures have more or less remained unchanged for the last 20 years<sup>4</sup>. Local failure is the most common cause of mortality and morbidity in these patients.

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In an attempt to improve local control and thereby survival, various chemotherapeutic agents have been tried concurrently with radiotherapy and cisplatin came out to be the most effective single agent. Radiotherapy concurrent with cisplatin has produced an absolute increase in the 5 year survival rate of 12% compared with radiotherapy alone <sup>5</sup>, clearly a step forward in the treatment of locally advanced cervical carcinoma. Among the schedules used in randomized trials, weekly cisplatin at a dose of 40 mg/m<sup>2</sup> with concurrent radiotherapy seems to be the best therapeutic option.

Gemcitabine is a drug, which has shown definite radiosensitizing properties in preclinical trials <sup>6</sup> including human cervical carcinoma cell lines <sup>7</sup>. When used in combination with cisplatin for recurrent and metastatic diseases, gemcitabine has produced a response of greater than 40% <sup>8</sup>.

Zarba et al <sup>9</sup> reported a phase I-II study of cervical cancer patients with stage IIB to IVA disease using standard dose of 40 mg/m<sup>2</sup> of cisplatin plus escalating doses of gemcitabine starting at 75mg/m<sup>2</sup> with 25mg/m<sup>2</sup> increment in successive cohorts of three patients. They recommended a weekly dose of gemcitabine of 125 mg/m<sup>2</sup> when used in combination with cisplatin along with concurrent radiotherapy.

On the basis of these observations, we undertook this single institution, phase-II, nonrandomized study to evaluate the antitumor activity and toxicity of gemcitabine-cisplatin combination and concurrent radiotherapy for untreated locally advanced cervical carcinoma patients. Primary aim of this study was to determine the efficacy in achieving loco-regional control and to evaluate the toxicity of the concurrent therapy.

## Methods

Sixty-seven patients participated in the current study conducted from November 2003 to July 2005. The inclusion criteria were:

1. Age between 25 and 65 years.
2. Histologically proved squamous, adenosquamous or adenomatous carcinoma of the uterine cervix of FIGO stage IIB to IVA. The participating gynecologists did the clinical staging. During the study period we received a few stage IV A cases, but none could be included in the study due to very poor general condition (Kamofsky performance status <70) and/or paraaortic lymphadenopathy, and/or unacceptably low hematological parameters.
3. No detectable para-aortic lymphadenopathy as assessed by ultrasonography.

4. Normal chest x-ray.
5. Karnofsky performance status  $\geq 70$ .
6. Hematology, and renal and hepatic functions as follows:
  - i) Hemoglobin  $\geq 10$  g/dL.
  - ii) Total leukocytes  $\geq 4000/\text{mm}^3$ .
  - iii) Platelet count  $\geq 1,00,000/\text{mm}^3$
  - iv) Serum bilirubin  $\leq 1.5$  times the normal upper limit.
  - v) Serum creatinine  $\leq 1.5$  times the normal upper limit.
7. Minimum education level of Class VIII.

The exclusion criteria were:

- a) Psychiatric illness.
- b) Previous or concomitant other malignant disease.
- c) Serious systemic illness.

Signed informed consent was obtained. Every patient had the liberty to withdraw herself from the study at any time she wished without hampering her treatment.

Cystoscopy, proctosigmoidoscopy and intravenous pyelography were done when indicated. Before starting treatment, all patients were given a course of broad spectrum antibiotics besides prophylactic oral iron supplement till the end of therapy. Psychological assessment was also done before accepting a patient in the study. The study was approved by our ethics committee.

## Radiotherapy

EBRT: External beam radiotherapy was administered to the whole pelvis to a total dose of 5000 cGy in 25 fractions over a period of 5 weeks (Monday to Friday of every week) using a Cobalt-60 machine at a source-skin distance of 80 cm. Usually parallel opposing antero-posterior and postero-anterior fields were preferred, but when the interfield distance exceeded 18 cm, a four field box technique was used. The usual field margins for the anterior and posterior fields were L<sub>4</sub>-L<sub>5</sub> inter space (superiorly), bottom of the obturator foramen or 2 cm below the lowest extent of the disease (inferiorly) and 1 cm beyond the lateral margins of the bony pelvic wall (laterally). Lateral fields, when applied, had their anterior margin at the anterior edge of the symphysis pubis and the posterior margin at the S<sub>2</sub>-S<sub>3</sub> inter space.

ICRT : Intracavity brachytherapy was started 1 week after completion of the EBRT course. It was delivered by tandem and ovoid applicators using high dose rate (HDR) Iridium - 192 sources. Three applications of 700 cGy each to point-A (a reference point 2 cm superior and 2 cm lateral to the

external cervical os) were done 1 week apart. Rectum and urinary bladder were pushed away as far as possible from the ovoids using rectal separator and vaginal gauze packing.

#### Chemotherapy

Chemotherapy was administered every week during the EBRT beginning from the first day of radiation. Chemotherapy infusion was started 3 hours before the schedule time of radiation on out patient basis via a peripheral vein as follows:

- i. Antiemetic prophylaxis with 8 mg dexamethasone and 3 mg granisetron, both intravenously very slowly.
- ii. Hydration with 500 mL normal saline in 30 minutes.
- iii. Cisplatin (40 mg/m<sup>2</sup> of body surface area) diluted in 500 mL normal saline containing 62.5 mL of 20 % mannitol infused over a period of one hour.
- iv. Normal saline 250 mL infused in 15 minutes followed by 250 mL normal saline charged with gemcitabine (125 mg/m<sup>2</sup> of body surface area) infused in 30 minutes.

Radiotherapy was delivered after a rest period of 30 minutes.

Five courses of chemotherapy were given to each patient during EBRT.

#### Toxicity assessment and management

Hematological and renal parameters were assessed every week (preferably on Friday) during EBRT and ICRT. Non-hematological toxicities were assessed by the radiotherapist at the same frequency and earlier, if needed. All toxicities were scored as per ECOG (Eastern Co-operative Oncology Group) scale. Dose modification of drugs or radiation was not allowed. Blood transfusion or colony stimulating factor injection was allowed in case of Grade 3 or Grade 4 hematological toxicities, as indicated. Grade 2 gastrointestinal toxicities were controlled by dietary modifications and drugs were given in grade 3 or 4 toxicities. Treatment may be delayed week by week in case of any uncontrolled Grade 3 or Grade 4 toxicity.

#### Posttreatment assessment

On completion of therapy, patients were assessed after 6 weeks by physical and pelvic examinations, and whenever needed by abdominal ultrasonography, chest x-ray, cystoscopy, and proctosigmoidoscopy. Subsequent assessments were done 12 weekly for the next 2 years,

#### End point and evaluation of treatment

The primary end point of the study was clinical response rate (loco-regional control), which was evaluated by the same gynecologists who made the staging and also by the

investigations as mentioned above. At the same time we tried to find out whether or not this form of management is tolerated by our patients, whose general condition is not so good as that of women in developed countries.

The response rates were scored as per WHO guidelines. Complete response was defined as disappearance of all clinical diseases for 1 month after completion of therapy. Partial response and stable disease were defined as >50% and <50% reduction of tumor size for 1 month after treatment completion respectively. An increase of tumor size of >25% has been considered as progressive disease.

**Table 1. Pretreatment patient characteristics (n=67).**

Characteristic	
Median age (years)	37 (Range 29 to 64).
Histologic type	
Squamous	58 (86.5 %)
Adenosquamous	04 (05.9 %)
Adenomatous	05 (07.6 %)
FIGO stage	
IIB	18 (26.8 %)
IIIA	03 (04.5 %)
IIIB	46 (68.7 %)
IVA	Nil
Karnofsky' performance status	
70	13 ( 19.5 %)
80	20 ( 29.8 %)
≥ 90	34 ( 50.7 %)
Median hemoglobin (g/dL)	11.3 (Range 8.7 to 13.4)

## Results

*Patient compliance, toxicity assessment and management:* Table 1 gives patient characteristics. Four patients withdrew themselves from the study during EBRT, mainly due to diarrhea. These four patients were treated with radiotherapy alone after controlling the diarrhea and were excluded from the response analysis though they were included in the toxicity assessment.

Table 2 shows the incidences of acute toxicities (as per ECOG criteria) during treatment. Five of the 67 patients developed Grade 3 leukopenia, all near the end of EBRT, and all of them received colony stimulating factor (Filgrastim) injection to prevent the progression of the leukopenia to grade 4. Similarly though all patients were receiving oral iron preparations from the beginning of therapy, all the four patients with grade 3 anemia were also given blood transfusion. Diarrhea was one of the most frequent nonhematological complication and though all

**Table 2. Acute toxicities as per ECOG criteria (n=67).**

	<b>Grade 0</b> (None)	<b>Grade 1</b> (Mild)	<b>Grade 2</b> (Moderate)	<b>Grade 3</b> (Severe)
Leukopenia	29 (44 %)	22 (33 %)	11 (16 %)	05 (07%)
Thrombocytopenia	24 (36 %)	37 (55 %)	06 (09 %)	00
Anemia	15 (22 %)	36 (54 %)	12 (18 %)	04 (06 %)
Nausea and vomiting	17 (25 %)	42 (63 %)	08 (12 %)	00
Diarrhea	17 (25 %)	36 (54 %)	10 (15 %)	04 (06 %)

No patient had grade 4 or life threatening toxicity

patients of grade 1 diarrhea were advised dietary modifications and plenty of oral rehydration solution, medications had to be given to the four patients with Grade 3 diarrhea. Three of these four patients were also suffering from grade 3 anemia and these four patients withdrew themselves from the study, leaving behind 63 patients for analysis of results. Almost all patients developed some form of vaginal mucositis but it became very troublesome in only six patients for whom local application of hydrocortisone suspension had to be prescribed.

The estimated period of completion of radiotherapy (EBRT + ICRT) was 57 to 59 days. Forty-nine (78%) patients completed it within the stipulated period, nine (14%) within 64 days and five (08 %) within 71 days.

### Response

Sixty-three patients were available for treatment response evaluation. At 3 months after completion of treatment, 61 out of 63 (97%) patients achieved an objective response – 42 (67%) patients had complete response, 16 (25%) had partial response, three (05%) had stable disease and two (03%) had progressive disease. At a median follow up of 10.5 months (range 3 to 16 months), 38 (60%) patients had no evidence of disease, 15 (24%) had pelvic failure or persistent local disease only, one (02%) had lung metastasis and four (06%) had paraaortic lymph node metastasis in addition to pelvic disease. During this period five patients (08%) were lost to follow up despite all our attempts to trace them. Responses as per disease stage are shown in Table 3.

**Table 3. Stagewise response to treatment.**

Stage	At 3 months (n =63)				At 10.5 months (Median) (n = 58)			
	CR	PR	SD	PD	CR	PF	LM	PA
II B	13	03						
	01	01	12	06	00	00	00	00
III A	02	01						
	00	00	02	01	00	00	00	00
III B	27	12						
	02	01	24	08	01	04	00	04

CR: Complete response PR:Partial response SD: Stable disease PD: Progressive disease PF: Pelvic failure or persistent local disease  
LM: Lung metastasis PA: Paraaortic lymph node metastasis

## Discussion

Carcinoma of the uterine cervix is a curable disease if detected at an early stage as has been proved in developed countries. But in developing countries, due to lack of health consciousness combined with virtual absence of screening programs most of the patients present with a locally advanced disease and uncontrolled pelvic disease is the cause of death in most of them. Thus loco-regional control is of paramount importance to cervical carcinoma patients in developing countries.

Radiation therapy is the treatment of choice for most patients with locally advanced (FIGO stage IIB to IVA) disease. The success of treatment depends upon a careful balance between EBRT and ICRT that optimizes the dose to the tumor and normal tissues as well as upon the overall duration of treatment. But as survival rates have remained more or less constant for the past 20 years<sup>3</sup>, and are disappointing for IIB and IVA diseases, various chemotherapeutic drugs either in neoadjuvant form or in concomitant form have been tried along with radiotherapy.

Concurrent chemo-radiation is a novel kind of approach. Both treatments interact to increase the tumor cell death without delaying the duration of radiotherapy and thus minimizing the repopulation of the malignant cells. Though various radio-sensitizers have been evaluated, cisplatin has proved to be the most effective radio-sensitizer.

Rose et al<sup>10</sup> reported the results of GOG-120 trial in which a course of standard pelvic radiotherapy was combined with one of the three concurrent chemotherapy regimens – (i) cisplatin alone (40 mg / m<sup>2</sup> weekly), (ii) cisplatin (50 mg/m<sup>2</sup> on days 1 and 29) plus 5-FU (4 g / m<sup>2</sup> as 96 hours infusion on days 1 and 29) plus hydroxyurea (2 g/m<sup>2</sup> orally twice weekly), or (iii) hydroxyurea alone (3 g/m<sup>2</sup> orally twice weekly) in patents with FIGO II B to IVA cervical carcinoma. At a median follow up of 35 months, survival curves for the two cisplatin groups were almost identical and both were statistically superior to the survival curve of the hydroxyurea alone group. However toxicities were much more in the combined drug arms than in the cisplatin alone arm.

In 1999 Keys et al<sup>11</sup> reported the results of the GOG-123 study in which 369 patients with bulky stage IB disease and without any evidence of paraaortic lymph node metastasis were randomized between weekly cisplatin (40 mg/m<sup>2</sup>) and radiation versus radiation only. Patients underwent hysterectomy 3 - 6 weeks after completion of radiation. At a median follow up of 36 months, local recurrence and distal metastasis rates were 9% and 21% and 12% and 16% respectively, both in favor of concomitant arm.

In 2001, Hernandez et al<sup>7</sup> exposed six cervical cancer cell lines to gemcitabine. They concluded that gemcitabine was cytotoxic in some of these cell lines and cytostatic in others. Gemcitabine showed a radio-sensitizing effect in these cells and was also found to effectively synergise with cisplatin.

Gemcitabine was first introduced in neoadjuvant approach. Lopez-Graniel et al<sup>12</sup> evaluated the feasibility, technical aspect and clinical results of surgery after induction of chemotherapy in 41 patients with IB<sub>2</sub> to IIB cervical carcinoma disease. All patents received three cycles of induction chemotherapy at 21 days interval with cisplatin (100 mg/m<sup>2</sup> on Day-1) and gemcitabine (1000 mg/m<sup>2</sup> on Days 2 and 8) followed by surgery or concomitant chemo-radiation. They concluded that type III radical hysterectomy is feasible in locally advanced cervical cancer patients who respond to chemotherapy and at a median follow up of 20 months disease free and over all survival rates were 59 % and 91 % respectively.

As phase I studies testing the combination of cisplatin and gemcitabine with concurrent radiotherapy in pancreatic cancer<sup>13</sup> and non-small-cell lung cancer<sup>14</sup> showed different maximum tolerated doses, Zarba et al<sup>9</sup> undertook a phase I-II study of weekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical cancer patients. Along with radiotherapy, cisplatin was administered at a fixed dose of 40 mg/m<sup>2</sup> weekly and gemcitabine was added at a starting dose of 75 mg/m<sup>2</sup> and escalated with a 25 mg/m<sup>2</sup> increment in successive cohort of three patients. Of the 36 patients with FIGO stage IIB to IVA disease who entered the study, the 3 year disease free survival rate was 67 % and overall survival rate was 72 %. They recommended that the dose of gemcitabine should be 125 mg/m<sup>2</sup> when used along with cisplatin and concurrent radiotherapy.

In the present study toxicities were mostly hematological and of these anemia was the commonest. Sixteen patients (24%) developed grade 2 and 3 anemia and had to receive blood transfusion in addition to oral iron supplementation. Probably comparatively low economic condition resulting in poor general condition of the cervical cancer patients in our country is the cause of this high incidence of anemia and other hematological toxicities met in the present study. In a similar study, Dueñas-González<sup>15</sup> et al found no RTOG (Radiation Therapy Oncology Group) grade 3 or 4 anemias among their 43 patients. At the same time, it should be borne in mind that the median hemoglobin level of their patients was 13.4 g/dL whereas median hemoglobin level of our patients was only 11.3 g/dL. Diarrhea was the most common nonhematological toxicity of our patients and all the four patients with grade 3 diarrhea had withdrawn themselves from the study. Repeated pelvic infection of our women,

particularly from the rural areas, leading to adherence of the gut to the lower pelvis may be the cause of this diarrhea.

As many of our patients are illiterate or barely literate, a minimum level of education (Class VIII standard) was fixed by us to be acceptable for the study. We presumed that a minimum level of education and intelligence are required to convince the patients the need of the study, that the acute toxicities though troublesome are temporary and do pass off after completion of the treatment, and the importance of long follow up. Psychological counseling of the patients also helped a lot in this respect.

At a median follow up of 10.5 months (after completion of treatment), 60 % of our patients were disease free though the complete response rate was 67 % at 3 months. It is true that the follow up period is comparatively short but the follow up is still going on. Our results are somewhat inferior to those of Zarba et al <sup>9</sup> (3 year disease free survival – 67 %) and Dueñas-González et al <sup>15</sup> (Pathologic complete response rate – 77.5 %). At the same time it should be kept in mind that 47.2% of the patients in Zarba et al's <sup>9</sup> series had stage IIB disease and no patient of the Dueñas-González et al's <sup>15</sup> series had stage III or IV disease. On the other hand about 40% patients of the gemcitabine - cisplatin arm of Dueñas-González et al's <sup>15</sup> study had IB<sub>2</sub> - IIA disease. Whereas 73.2% of our patients had stage III disease and it is well established that advanced stage disease and low hemoglobin level are two bad prognostic factors for cervical carcinoma.

## Conclusion

Concurrent chemo-radiotherapy with cisplatin - gemcitabine has shown promising results in locally advanced cervical carcinoma. Most of the toxicities can be treated on outpatient basis minimizing the cost of patient management. Both the factors are very important in a developing country like ours, with a huge number of cervical carcinoma patients mostly in advanced stages.

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