

## Weekly versus Tri-weekly Cisplatin Concurrent with Radiotherapy in the Treatment of Locally Advanced Carcinoma Cervix: A Prospective Study

### Abstract

**Context:** Different schedules of concurrent chemotherapy with definitive radiotherapy in locally advanced carcinoma cervix. **Aims:** The aim is to evaluate toxicity, compliance, and response of weekly versus tri-weekly cisplatin given concurrently with radiotherapy in locally advanced squamous cell carcinoma cervix. **Subjects and Methods:** One hundred and ten newly diagnosed histopathologically confirmed squamous cell carcinoma cervix patients with International Federation of Gynecologists and Oncologists stage IIB to IVA were randomly distributed among study group receiving 75 mg/m<sup>2</sup> of cisplatin every 3 weeks for three cycles and control group receiving 40 mg/m<sup>2</sup> of weekly cisplatin for six cycles. **Results:** Patients in both the arms tolerated treatment well. At the time of completion of chemoradiotherapy, 83.63% of patients of the study group and 80% of the control group had a complete response whereas 16.37% of study and 20% of the control group had a partial response, both statistically insignificant ( $P > 0.05$ ). Compliance was similar in both the groups. The average time to complete radiotherapy was 54.63 days in the study group and 51.34 days in the control group. In the study group, 87.27% of patients completed all cycles of tri-weekly chemotherapy, whereas, in control group, 80% completed all 6 cycles of weekly chemotherapy. The difference was not statistically significant ( $P = 0.30$ ). Toxicity in terms of vomiting, grade 3–4 leukopenia and neutropenia were more in the study group which was statistically significant ( $P < 0.001$ ,  $P = 0.04$ , and  $P = 0.03$ , respectively). **Conclusions:** Although the 3-weekly cisplatin schedule has longer intervals and sounds convenient, the weekly cisplatin regime shows lower hematologic toxicity with similar disease response and compliance.

**Keywords:** Cervical cancer, concurrent chemoradiation, Cisplatin, external-beam radiotherapy, International Federation of Gynecology and Obstetrics, high dose rate intracavitary brachytherapy

### Introduction

Cervical cancer is the second most common cancer diagnosed in women in India.<sup>[1]</sup> About 122,844 new cervical cancer cases are diagnosed annually in India.<sup>[2]</sup> At our center, carcinoma cervix is the most common cancer among females. Patients usually present to us with International federation of Gynecology and Obstetrics (FIGO) stage IIB, III and IV; in which Concurrent Chemo-Radiotherapy (CCRT) plays a major role in the management.<sup>[3,4]</sup>

### Subjects and Methods

The present prospective study was carried out at Sawai Man Singh Medical College and attached group of Hospitals, Jaipur, Rajasthan from January 2014 to June 2015 with a median follow up of 33 months. 110 histopathologically confirmed newly diagnosed cases of

squamous cell carcinoma of cervix FIGO stage IIB to IVA with ECOG performance status 0–2 were randomised into study and control groups, with 55 patients in both groups. All patients were younger than 70 but older than 18 years with hemoglobin  $\geq 9$  g%, absolute neutrophil count  $>1500$ /uL, platelet count  $>1,00,000$ /uL, serum creatinine level  $<1.4$  mg/dl and serum bilirubin  $<2$  times the normal upper unit. Patients with other than squamous pathology, history of previous radiotherapy or surgery for the same malignancy, second malignancy, distant metastasis, other uncontrolled comorbidities, and pregnancy were excluded from the study.

### Chemotherapy

All patients who were enrolled in the study group were planned to receive injection cisplatin with dose of 75 mg/m<sup>2</sup>

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intravenously on day 1, 22, and 43 of radiotherapy, for a total of three courses. Those who were enrolled in the control arm were planned to receive injection cisplatin with dose of 40 mg/m<sup>2</sup> intravenously on day 1, 8, 15, 22, 29, and 36 of radiotherapy, for a total of six courses.

### Radiotherapy

Combined external-beam radiotherapy (EBRT) and high dose rate intracavitary brachytherapy (HDR ICBT) was used for the treatment of patients. The primary tumor and regional lymphatics were treated with 45–50.4 Gy in conventional fractionation at 1.8 Gy per fraction over Seimens Onco Expression Linear Accelerator using three-dimensional conformal radiotherapy technique with 15 MV beam energy. The first HDR ICBT was performed toward the latter part of EBRT when sufficient tumor regression was noted to permit satisfactory applicator geometry. This was usually after the 3<sup>rd</sup> week of EBRT and additional EBRT was delivered with a central shield. On the day of ICBT, neither EBRT nor chemotherapy was prescribed. The recommended total point A dose combining EBRT with ICBT was 80 Gy for small volume cervical tumors and 85–90 Gy for large volume tumors. To avoid the negative impact of treatment prolongation, the overall treatment time was intended to be kept <8 weeks.<sup>[5,6]</sup>

### Evaluation of patients

All patients were clinically examined weekly during the treatment for any complaints. Hemogram and biochemical investigations were performed and noted before giving chemotherapy. The clinical appearance of the primary tumor at the initiation of treatment was noted. The regression of primary tumor during the treatment was assessed and noted biweekly. Any delay causing treatment interruption was also noted and necessary gap correction for radiotherapy was done. Chemotherapy was withheld during radiotherapy interruptions, but radiotherapy was continued in spite of chemotherapy being discontinued due to hematological toxicities. At the completion of treatment and subsequent follow up, the disease response was assessed. The results of study group were analyzed and compared with control group in terms of compliance, toxicities, and tumor response. Response was assessed as per the WHO Criteria. Acute toxicities were assessed as per the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring criteria. Chemotherapy induced toxicities such as nausea, vomiting, renal and hematological toxicities were assessed as per the Common Terminology Criteria for Adverse Events (v4.03), National Cancer Institute (USA). Patients were evaluated every month on follow up with detailed clinical examination to assess local disease response and to note any bladder/bowel symptom. Hematological tests and imaging studies were done wherever indicated.

### Statistical analysis

This was an open-label, randomized trial with 1:1 allocation. The randomized assignment was done using a chit in box method with replacement. The categorical clinical characteristics between the two treatments were compared using Chi-square ( $\chi^2$ ) test. Data were analyzed using Statistical Package for Social Sciences (SPSS) software trial version 20.0 (IBM Corp., Armonk, New York, USA).

### Results

In the present study, the patient and tumor characteristics were identical in the two groups [Table 1]. In both the groups, patients were in the age group of 30–70 and majority of them were in their 4<sup>th</sup> and 5<sup>th</sup> decade of life. Mean age of presentation was 49.36 and 49.43 years for study and control group, respectively. More than two-third of the patients belonged to the rural background in both the groups. All the patients included in the study were having ECOG performance status score up to 2. The hemoglobin of all patients included in the study was equal or above 9.0 g%, mean hemoglobin at presentation was 10.56 g% and 10.60 g% for study and control group, respectively. Only histopathologically proven squamous cell carcinoma patients were included in this study. The distribution of patients according to the histological differentiation of primary tumor revealed moderately differentiation as the most common pattern of differentiation. Among the study group, 78.2% and in the control group, 81.8% had moderately differentiated tumor. The most common stage of presentation was FIGO stage IIB with 54.5% in the study group and 50.9% in control group.

Treatment related toxicities are shown in Table 2 and Figure 1. In the study group, 10 patients (18.2%) had grade 1 skin reactions as compared to 20 (36.4%) in the control group. 34 (61.8%) and 11 (20%) patients in the study group and 26 (42.8%) and 7 (12.7%) in the control group had grade 2 and grade 3 skin reaction,

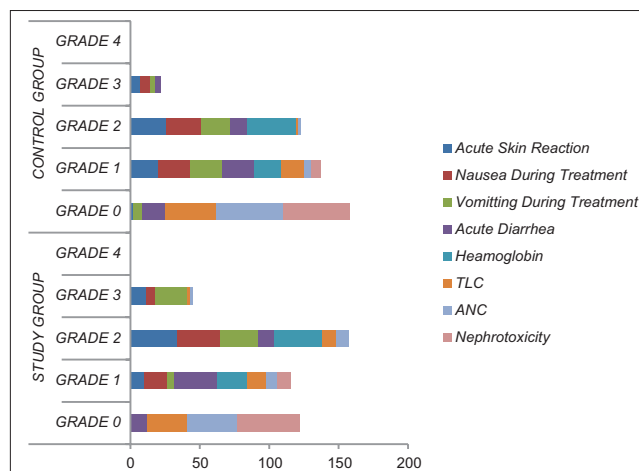


Figure 1: Worst Acute Toxicity During Treatment

**Table 1: Patient, tumour and treatment characteristics**

	Study group, n (%)	Control group, n (%)	P value
Age (years)			
≤40	9	13	0.15
41-50	25	18	
51-60	16	12	
61-70	5	12	
Geographic distribution			
Rural	38 (69)	37 (67.3)	0.84
Urban	17 (31)	18 (32.7)	
ECOG performance status			
0	0	0	0.54
1	50 (91)	48 (87.3)	
2	5 (9)	7 (12.7)	
FIGO stage			
IIB	30 (54.5)	28 (50.9)	0.70
IIIA	2 (3.6)	1 (1.9)	
IIIB	22 (40)	23 (41.8)	
IVA	1 (1.9)	3 (5.4)	
Differentiation of squamous cell carcinoma			
Well differentiated	10 (18.2)	7 (12.7)	0.68
Moderately differentiated	43 (78.2)	45 (81.8)	
Poorly differentiated	2 (3.6)	3 (5.5)	
Duration of radiotherapy (weeks)			
≤8	48	52	0.18
>8	7	3	

ECOG – Eastern cooperative oncology group; FIGO – International federation of gynecology and obstetrics

**Table 2: Worst acute toxicity during treatment**

Toxicity	Study group					Control group					Statistics
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	P Value
Acute skin reaction	0	10	34	11	0	2	20	26	7	0	0.06
Nausea during treatment	0	17	31	7	0	0	23	25	7	0	0.46
Vomiting during treatment	0	5	27	23	0	7	23	21	4	0	<0.001
Acute diarrhea	12	31	12	0	0	16	23	12	4	0	0.12
Haemoglobin	0	21	34	0	0	0	20	35	0	0	0.84
TLC	29	14	10	2	0	37	16	2	0	0	0.04
ANC	36	8	9	2	0	48	5	2	0	0	0.03
Nephrotoxicity	45	10	0	0	0	48	7	0	0	0	0.43

TLC – Total leukocyte counts; ANC – Absolute neutrophil counts

**Table 3: Follow-up status**

Treatment response	Study group (n)				Control group (n)				Statistics
	Complete response	Partial response	No change	Progressive disease	Complete response	Partial response	No change	Progressive disease	P value
End of treatment	46	9	0	0	44	11	0	0	0.63
6 month follow up	50	5	0	0	50	5	0	0	1.00

respectively ( $P = 0.06$ ). For nausea, in the study group 17 (30.9%) of the patients had grade 1 reactions as compared to 23 (41.8%) in the control group. 31 (56.4%) in the study group and 25 (45.5%) in the control group had

grade 2 reaction. The incidence of grade 3 was 7 (12.7%) and 7 (12.7%) in the study group and control group, respectively ( $P = 0.46$ ). The vomiting during the treatment was more in the study group which was statistically significantly  $P < 0.001$ . In the control group, 30 (54.5%), 21 (38.18%) and 4 (7.27%) patients had grade 1, 2, and 3 vomiting, respectively, as compared to 5 (9.09%), 27 (49.09%), and 23 (41.8%) patients in the study group. The incidence of acute diarrhea during treatment was seen more in study group; 31 (56.4%), 12 (21.8%), and 0 (0%) had grade 1, 2, and 3, respectively compared to control group having 23 (41.8%), 12 (21.8%), and 4 (7.2%) grade 1, 2, and 3 diarrhea, respectively. There is no statistical difference in incidence of acute diarrhea between the study and control groups ( $P = 0.12$ ).

As far as hematological toxicities are concerned, in the study group 21 (38.2%) had grade 1 and 34 (61.8%) had grade 2 anemia, whereas in control group, 20 (36.4%) had grade 1 and 35 (63.6%) had grade 2 anemia ( $P = 0.84$ ). For total leukocyte counts, study group had more grade 2 (10 [18.2%]) and grade 3 toxicity (2 [3.6%]) compared to control group having only 2 (3.6%) grade 2 toxicity. 14 (25.5%) and 16 (29.09%) had grade 1 toxicity in study and control group, respectively. This difference is statistically significant, showing more toxicity in the study group compared to control group,  $P = 0.04$ . Similar to total leukocyte count, absolute neutrophil count showed the same pattern of toxicity profile. 36 (65.5%) and 48 (87.3%) had no toxicity, 8 (14.5%) and 5 (9.09%) had grade 1, 9 (16.4%) and 2 (3.6%) had grade 2 and 2 (3.6%) and none (0%) had grade 3 toxicity in the study and control group, respectively. This difference was statistically significant, more in the study group compared to control group ( $P = 0.03$ ). No nephrotoxicity was found in 45 (81.8%) in the study group and 48 (87.3%) in the control group, whereas 10 (18.2%) and 7 (12.7%) were found to have grade 1 toxicity in the study and control group, respectively ( $P = 0.43$ ). The audiometry report of all the patients was comparable to their pretreatment and post treatment reports, i.e., there was no increased hearing loss or ototoxicity found among all the patients in both study and control group.

Compliance of the treatment was defined in terms of completeness of chemotherapy and radiotherapy within the prescribed time limits. The American Brachytherapy Society recommends keeping the total treatment duration to <8 weeks, i.e., 56 days.<sup>[7]</sup> In the study group, the average time of completion of radiotherapy was 54.63 days, (range = 48–81 days), 48 (87.27%) patients completed their radiotherapy within 56 days (8 weeks) of starting treatment. Whereas in the control group, the average time was 51.34 days, (range = 48–60 days), 52 (94.54%) patients completed within the prescribed time of 56 days (8 weeks). This difference did not reach statistical significance ( $P = 0.18$ ).

Treatment response of disease of patients was done using the WHO criteria while on treatment and subsequent follow up. At the end of treatment, 46 (83.63%) of study group and 44 (80%) of control group had complete response (CR), 9 (16.37%) patients of study group and 11 (20%) patients of control group had partial response (PR) ( $P = 0.62$ ). At 6 months after completion of CCRT, both the study and control group had 50 (90.9%) CR and 5 (9.1%) PR rates ( $P = 1$ ). At last follow up, the disease-free survival was same for both the study and control group [Table 3].

## Discussion

In 1999, five large prospective randomized trials performed by the Gynecologic Oncology Group (GOG), RTOG, and the South-West Oncology Group demonstrated significant survival advantage and superiority in reducing risk of death by 30%–50% in cisplatin-based chemotherapy given concurrently with pelvic radiotherapy when compared to either radiotherapy alone or radiotherapy with concurrent nonplatinum containing chemotherapy. It was stated that cisplatin-based CCRT also decreased the relative risk of recurrence and the mortality. Among the previous five randomized clinical trials, two trials performed by the GOG used weekly cisplatin 40 mg/m<sup>2</sup>, whereas the other three trials used tri-weekly cisplatin at a dosage range of 50–75 mg/m<sup>2</sup> combined with 5-fluorouracil. Although recently reported meta-analysis studies also demonstrated 6% improvement in 5-year survival with cisplatin-based CCRT, the optimal cisplatin dose and dosing schedule are still undetermined. Hence, in this study, we tried to investigate the response, compliance and toxicity of weekly cisplatin 40 mg/m<sup>2</sup> and tri-weekly cisplatin 75 mg/m<sup>2</sup> administration concurrent with radiotherapy.<sup>[4,8-10]</sup>

The results of five randomized studies which included nearly 2000 patients were published in 1999, demonstrating that survival rate with CCRT based on cisplatin was superior to that obtained with radiation alone. Afterward, a meta-analysis based on 19 trials (17 published and two unpublished) including 4580 patients corroborated these findings, confirming that chemoradiation offers an absolute survival benefit of 12% at 5 years.<sup>[11]</sup> Thus, cisplatin-based CCRT was largely accepted as the standard of care for patients with locally advanced cervical cancer with FIGO stage IB2-IVA, except for patients with comorbidities who are radiated for stage IB1 or less. CCRT also showed significant benefit for local recurrence and the suggestion of a benefit for distant recurrence. Acute hematological and gastrointestinal toxicity was significantly higher in the CCRT group.<sup>[12]</sup> After years of studying multi-modality treatments as an alternative to radiation alone in randomized phase III trials, the standard treatment has changed to CCRT based on cisplatin.<sup>[13]</sup> Despite these encouraging results, there remains room for improvement as the 5-year survival of patients treated with CCRT ranges from nearly 80% in bulky IB tumors to only 25% in stage IVA disease.

Kato *et al.*<sup>[14]</sup> studied CCRT with weekly cisplatin in locally advanced cervical carcinoma and observed acute grade 3 leukopenia in 21% of the patients, and grade 3 gastrointestinal toxicity in 6%. No patient failed to complete the radiotherapy course because of toxicity. The 2-year local control and overall survival rate for all patients were 87.1% and 79.6%, respectively. In this study, they had more toxicity, may be due to less number of patients enrolled in the present study. Ryu *et al.*<sup>[15]</sup> in 2010 compared weekly versus tri-weekly cisplatin administered concurrently with radiotherapy in 104 locally advanced ca cervix patients. He found that all patients tolerated both treatments very well, with a high completion rate of scheduled chemotherapy cycles. There was no statistically significant difference in compliance between the two arms (86.3% in the weekly arm, 92.5% in the tri-weekly arm,  $P > 0.05$ ). Grade 3–4 neutropenia was more frequent in the weekly arm (39.2%) than in the tri-weekly arm (22.6%) ( $P = 0.03$ ). The overall 5-year survival rate was significantly higher in the tri-weekly arm (88.7%) than in the weekly arm (66.5%) (Hazard ratio 0.375; 95% confidence interval 0.154–0.914;  $P = 0.03$ ). So, they concluded that tri-weekly cisplatin 75 mg/m<sup>2</sup> chemotherapy concurrent with radiotherapy is more effective and feasible than the conventional weekly cisplatin 40-mg/m<sup>2</sup> regimen. Chumworathayi *et al.*<sup>[16]</sup> 2005 studied compliance of weekly versus 3-weekly cisplatin as an adjunct to radiotherapy in high-risk early stage cervical carcinoma after surgery using 40 mg/m<sup>2</sup> as weekly cisplatin dose for 6 cycles and 75 mg/m<sup>2</sup> tri-weekly cisplatin for 4 cycles and found statistically significant difference in neutropenia and hearing loss. In the present study, none of the patients had hearing loss, whereas the neutropenia was consistent with the findings. Ikushima *et al.*<sup>[17]</sup> in 2006 found severe hematological toxicity in 86% patients, grade 3 in 81% patients and grade 4 in 4.8% patients. Moderate or severe gastrointestinal toxicity occurred in 11 patients (52%), grade 2 in 10 patients (48%), and grade 3 in one patient (4.8%). All patients completed RT without interruption. This study had higher toxicity as compared to the present study, reason being lesser number of patients enrolled in the study done by them.

In the study, Chumworathayi *et al.*<sup>[16]</sup> have found 100% completion of chemotherapy but with delay in 30.3% cycles in the 3 weekly group and 12.9% cycles delay in the weekly group, which is statistically not significant. In their study, they have found that all patients completed their radiotherapy within time, the time frame in their study to complete radiotherapy was 10 weeks. This finding of chemotherapy completion was not consistent with the study. Although their study showed better compliance in the weekly group, it was not statistically significant. Moreover, their time period of completion of radiotherapy was 10 weeks which is different from the recommended duration of 8 weeks.

In a study by Kim *et al.*<sup>[18]</sup>, full planned CCRT was delivered to 55 (71%) patients. The incidence of acute

grade 3/4 hematologic toxicity was 26%. The CR rate was 91%. Four-year overall and progression-free survival rates were 67% and 66%, respectively, these results are consistent with results of the present study. Toita *et al.*<sup>[19]</sup> reported grade 3/4 leukopenia as the most common acute side effect (83%). The actuarial 3-year pelvic control rate, disease-free survival rate, and overall survival rate were 91%, 67%, and 79%, respectively; these results are consistent with the result of the present study.

## Conclusion

The present study shows that weekly cisplatin concurrent with radiotherapy is feasible and has same compliance and response rates as compared with tri-weekly cisplatin in patients with locally advanced cervical cancer. Despite the small number of patients in this single institutional study, there were statistically significant differences in vomiting and grade 3–4 leucopenia and neutropenia, associated more with tri-weekly cisplatin compared to weekly cisplatin.

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## Conflicts of interest

There are no conflicts of interest.

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