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A prospective randomized study to compare weekly versus tri-weekly cisplatin-based concurrent chemoradiation in the treatment of locally advanced carcinoma cervix

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ABSTRACT

Background: Concurrent chemoradiotherapy with cisplatin is the standard treatment for locally advanced carcinoma cervix. Cisplatin can be given either as weekly or a tri-weekly regimen with radiotherapy. However, there were few studies comparing both, so our study aimed at comparing weekly versus tri-weekly cisplatin-based chemoradiation in terms of loco-regional control and acute toxicity profile. **Aims and Objectives:** To compare the treatment response and acute toxicity profile of thse two concurrent chemotherapy schedule. **Materials and Methods:** Patients with non-metastatic, squamous cell carcinoma of uterine cervix International Federation of Gynecology and Obstetrics stage IB2-IVA were randomized into two arms-control arm patients received external beam radiotherapy (50Gy in 25 fractions over 5 weeks) with concurrent weekly cisplatin (40mg/m^2), and study arm patients received radiotherapy with same dose, along with tri-weekly concurrent cisplatin (75 mg/m^2) for two cycles. After that, all patients received brachytherapy 21 Gee/3 fractions, one fraction/week. All patients were followed up weekly during treatment and then monthly for at least a period of 6 months for evaluation of toxicity and treatment response. **Results:** Six weeks after treatment completion, complete treatment response was comparable in both the arms(43.33% vs. 46.67%, P = 0.35). Incidences of leucopenia were significantly high in weekly cisplatin arm (P = 0.002).Nephrotoxicity of higher grade was also numerically more in control arm (P = 0.654). However, treatment compliance was better in tri-weekly cisplatin arm, reflected by reduced treatment interruptions (46.67% vs. 53%). **Conclusion:** Tri-weekly cisplatin-based concurrent chemoradiation is equally effective as weekly cisplatin-based approach with comparable acute toxicity in treatment of carcinoma cervix.

Key words: Carcinoma cervix; Chemoradiotherapy; Weekly cisplatin; Tri-weekly cisplatin

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INTRODUCTION

According to GLOBOCAN2020, carcinoma cervix is the second most common malignancy among Indian women and it has been estimated that about 1.23 lakhs of new cases occur in India every year.[1]

Various prospective studies have reported a 10–15% increase in local control and survival with the addition of concurrent cisplatin-based chemotherapy to the conventional radiotherapy. On the basis of the results of five randomized clinical trials (GOG-85, Radiation therapy oncology group [RTOG]-9001, GOG-120, GOG123, and SWOG-879), which consistently showed improved survival in patients treated with cisplatin-based chemoradiation, the U.S. National Cancer Institute announced that consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiotherapy

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for the treatment of cervical cancer.[2-6] The risk of death from cervical cancer was decreased by 30–50% with the use of concurrent chemoradiation therapy.[3-8] A meta-analysis of 18 trials with concurrent chemotherapy and radiation in patients with cervical cancer concluded that concomitant chemoradiotherapy improved overall and progression-free survival and reduced local and distant recurrence in patients with cervical cancer.[9] Concomitant chemoradiation therapy produced a 12% absolute increase in survival with greater evidence of benefit in the trials using platinum-based chemotherapy than in those with non-platinum-based chemotherapy.[10] Based on these observations, the International Federation of Gynecology and Obstetrics (FIGO) recommended concurrent chemo-radiation as the standard primary treatment of cancer cervix (FIGO Stage IB-IVA) in2000.[11]

Although cisplatin is the mainstay of concurrent chemotherapy along with radiotherapy, the optimal dose and dosing schedule are still undetermined.[7,8] However, in light of the results of various clinical trials, two dosing schedules, standard weekly 40mg/m^2 and tri-weekly 75mg/m^2, are mostly used. However, despite the possible advantages of tri-weekly cisplatin 75mg/m^2, which offers an increased peak concentration, few clinical trials till date have directly compared these weekly and tri-weekly schedules as per our knowledge.[11] Hence, we designed this study to compare weekly cisplatin with tri-weekly cisplatin with radiotherapy in the treatment of locally advanced cervical cancer to compare response rate, local control, and acute toxicity profiles.

Aims and objectives

1. To compare the local response rate between radiotherapy with weekly cisplatin and radiotherapy tri-weekly cisplatin.
2. To compare the acute toxicity profile of weekly and tri-weekly concurrent cisplatin.

MATERIALS AND METHODS

It was a double arm, single institutional prospective, and comparative study in patients with histologically confirmed squamous cell carcinoma uterine cervix of FIGO stage IB2-IVA, aged between 20 and 70 years having adequate hepatic, renal, hematological parameters, and an ECOG score of 0–2. Patients who underwent hysterectomy or radical surgery, recurrent cervical carcinoma, previous history of any other malignancy, or chemotherapy or radiotherapy were excluded from the study.

Study technique

Eligible patients were selected using above-mentioned inclusion and exclusion criteria's and randomized into two groups:

1. CONTROL ARM (weekly cisplatin):In this arm, patients were treated with concurrent weekly cisplatin (40mg/m^2) for five cycles along with external beam radiotherapy.
2. STUDY ARM (tri-weekly cisplatin):In this arm, patients were treated with concurrent tri-weekly cisplatin (75mg/m^2)for two cycles on day 1 and 22 along with EBRT.

In both the arms, radiation dose was 50 Gy in 25 fractions over 5 weeks.

After completion of EBRT, patients of both arms received intracavitary brachytherapy for three fractions of 7 Gy every week for 3 weeks.

Radiotherapy technique

Telecobalt machine (Theratron 780E) was used to deliver external beam radiotherapy with conventional 2-dimensional fields based on anatomical landmarks.

Radiation portals were –

1. Two antero-posterior and postero-anterior (AP-PA) portals OR
2. Four field technique(AP-PA and Two lateral pelvic fields).

Follow-up

All patients were followed up weekly during treatment and then monthly for at least a period of 6 months. Acute toxicities (dermatological, gastrointestinal, genitourinary, and hematological toxicities including anemia, leucopenia, neutropenia, and thrombocytopenia) were assessed by weekly follow-up during treatment and were graded as per toxicity assessment tools–common terminology criteria for adverse events scale v5.0 and RTOG scoring. Treatment related toxicities were managed conservatively and treatment was interrupted when required.Treatment response was assessed using RECIST1.1 at the end of treatment and then monthly for next 6 months by gynecological examination and imaging (USG, CT scan pelvis/MRI pelvis) as and when required.

Ethical clearance

Ethical clearance was obtained from the Institutional Ethical Committee.

Statistical methods

Statistical analysis was conducted using IBM SPSS Statistics version 20.0 (SPSS Inc. Chicago, IL) and online GraphPad QuickCalcs application. For normally distributed data, the mean values between the two arms were compared for test of significance using unpaired t-test. Inter-arm mean differences were compared for test of significance using paired t-test. For comparing proportions of different events in between the two arms, Pearson's Chi-square test

was applied as test of significance. Any P<0.05 has been considered as significant.

RESULTS

A total of 60 patients were analyzed in this study with each arm having 30 patients (Figure 1). Both the arms were comparable in terms of baseline characteristics such as – age, performance status, stage of disease at presentation, and associated comorbidities (Table 1).

Response assessment

Loco-regional response at the end of treatment and at subsequent follow-ups was very much similar in the two treatment arms. Complete response at the end of treatment was 66.67% in the study (tri-weekly cisplatin) arm and 63.33% in the control (weekly cisplatin) arm and it was statistically not significant (P=0.260). Six months after the completion of treatment, CR in the study arm was 43.3%, and in the control arm, it was 46.6% although the difference was not statistically significant (P=0.35) (Figure 2).

Toxicity assessment

Grade III or more acute skin toxicity was33.33% in the study arm compared to 40% in the control arm. However, this was not statistically significant (P=0.205).

Genitourinary toxicity was numerically less in study arm (tri-weekly cisplatin) although the difference was statistically not significant (40% vs. 53%, P=0.530).

Numerically Grade III or more vomiting was higher in the weekly cisplatin containing control arm than in the tri-weekly cisplatin containing study arm (13.33 % vs. 6.67%) though it was statistically not significant (P=0.386).

Incidence of Grade III or more diarrhea was also higher in control arm than study arm (23.33% vs. 13.33%), but the difference was statistically not significant (P=0.313).

Among hematological toxicities, incidences of Grade II anemia were 40% in the study arm and 36.67% in the control arm, but incidences of Grade III anemia were 10 % in both the arms. Differences were not statistically significant (P=0.994).

Grade I leucopenia incidences were 53.33% in the study arm containing tri-weekly cisplatin and 16.67% in the control arm of weekly cisplatin. Grade III leucopenia incidences were also higher in the study arm (6.67% vs. 0%). These differences were statistically significant (P=0.002).

Grade II (23.33% vs. 13.33%) neutropenia was higher in the study arm, where as incidence of Grade III neutropenia was similar in both arms of the study (P=0.143) (Figure 3).

Two(6.67%) patients in the study arm and 4 (13.33%) patients in the control arm had nephrotoxicity of Grade II or more,though this was statistically not significant (P=0.654) (Table 2).

Total mean treatment duration in the study arm was 68 days and in the control arm; it was 68.4 days. The minimum time required to complete treatment (external beam radiotherapy and brachytherapy) was 58 days and maximum time was 80 days.

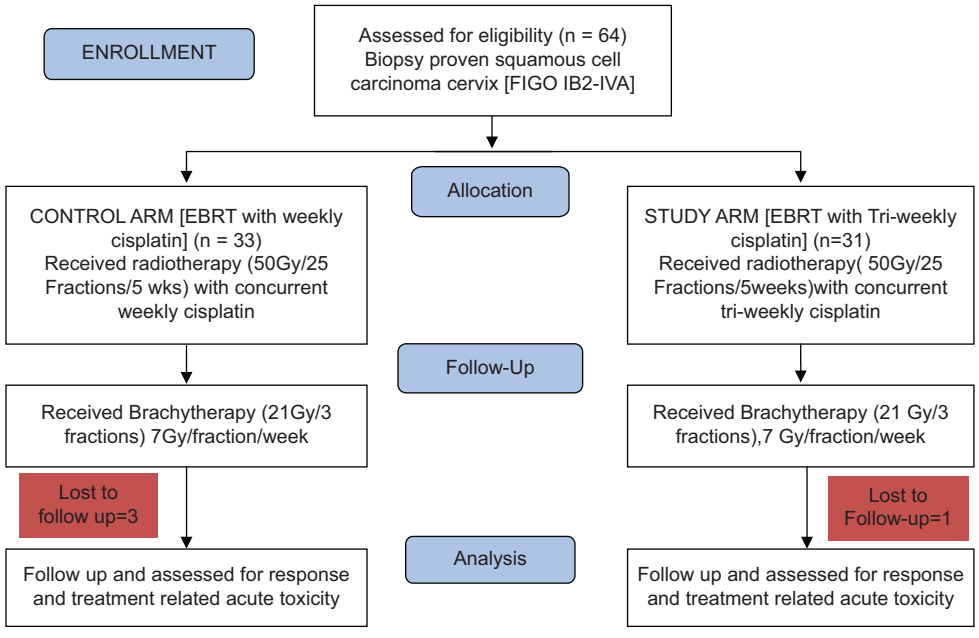

Figure 1: Consort flow diagram

Table 1: Distribution of baseline characteristics between two arms of the study

Characteristics	Arm of the study		Total sample size	P-value
	Control arm (n=30) (Weekly Cisplatin)	Study arm (n=30) (tri-weekly cisplatin)		
Mean age (in years)	53.13	52.10	60	0.634
Associated comorbidities				
Diabetes mellitus	06	04	60	0.686
Hypertension	01	02		
Nil	23	24		
Total	30	30		
FIGO stage				
IIA2	0	01	60	0.577
IIB	13	16		
IIIA	02	01		
IIIB	15	12		
Total	30	30		
Performance status (ECOG score)				
ECOG 1	21	22	60	0.774
ECOG 2	09	08		
Total	30	30		

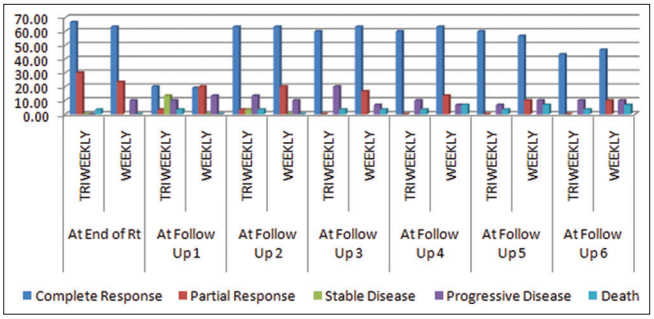

Figure 2: Comparison of response between two arms

Although statistically not significant, as per the continuity of treatment was concerned, numerically a smaller number of patients (46.67% vs. 53.33%) in the tri-weekly cisplatin arm interrupted treatment than weekly cisplatin arm.

DISCUSSION

In the present study, 60 patients with locally advanced squamous cell carcinoma of cervix were enrolled and randomized into two arms–study arm received concurrent chemoradiation with tri-weekly cisplatin and the control arm received concurrent chemoradiation with weekly cisplatin followed by brachytherapy in both the arms.

The mean age of the total patient population was 52.62 years. According to available literature, the peak age for cervical cancer incidence is 45–54 years in India.[2] The mean age of our study, thus, corresponds to the existing data from Indian population. The lowest age of presentation was 37 years and the maximum age at presentation was at 69 years suggesting that cervix cancer may occur in a young age as well as in old age.

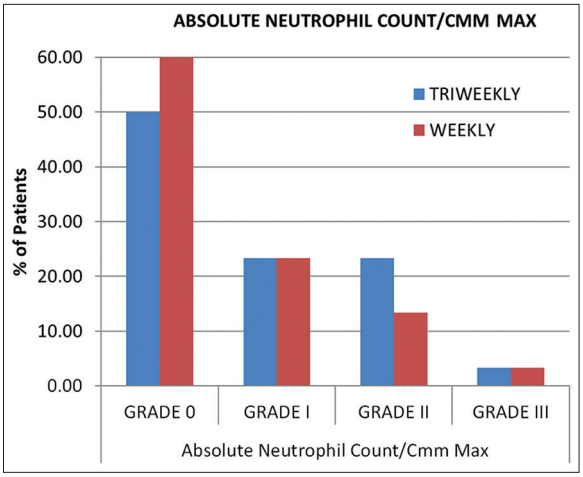

Figure 3: Neutropenia between two arms of the study

Other baseline parameters, including FIGO stage of disease at presentation, associated co-morbidities, and ECOG score, are the initiation of the study,which were comparable among the patients of both arms of the study.

Local response rates were assessed using the RECIST1.1 at the end of completion of treatment and then monthly for 6 months. Complete response (CR) at the end of treatment was 66.67% in the study (tri-weekly cisplatin) arm and 63.33% in the control (weekly cisplatin) arm, but it was not statistically significant (P=0.260). Six months after the completion of treatment CR in the study, arm was 43.3% and 46.6% in control arm. Both the arms had equal number of progressive disease (10%) and two deaths in control arm compared to one in the study arm, although the difference was not statistically significant (P=0.35).

In a study by Ryu et al., the compliance and toxicity of weekly concurrent cisplatin (40 mg/m^2) and tri-weekly

Table 2: Comparison of nephrotoxicity between two arms of the study

Arm	Nephrotoxicity			P-value
	Grade 0	Grade I	Grade II	
Study arm (Triweekly)	16	12	2	0.654
Control arm (Weekly)	16	10	4	

concurrent cisplatin (75 mg/m^2) in the treatment of carcinoma cervix was compared.[12] The study showed that tri-weekly cisplatin 75 mg/m^2 concurrent to RT increased 5-year survival rate significantly compared to weekly cisplatin 40 mg/m^2 in patients with locally advanced cervical cancer (66.5% in the weekly arm, 88.7% in the tri-weekly arm; HR=0.375, 95% CI: 0.154–0.914, P=0.03).[12] It also showed reduced hematological toxicity in tri-weekly arm.

Grade III or more diarrhea (23.33% vs. 13.33%) and vomiting (13.33% vs. 6.67%) incidents were numerically more in weekly cisplatin arm than tri-weekly cisplatin. Probably, this was due to repeated and frequent exposure to chemotherapy in weekly schedule. However,the differences were not statistically significant (P=0.313 and 0.386, respectively).

In the tri-weekly, arm 40% had Grade II anemia and 10% had Grade III anemia,while, in the weekly arm, 36.67% and 10% patients had Grade II and Grade III anemia, respectively. However, this slightly raised hematological toxicity in study arm was statistically not significant (P=0.994). It was seen that tri-weekly arm showed statistically significant leucopenia than in the weekly arm (P=0.002). It was probably due to high dose of cisplatin given in tri-weekly arm which resulted in higher peak plasma level achieved than lose dose cisplatin given in the weekly arm.

However, the risk of neutropenia was very much comparable between two arms. In the tri-weekly arm 23.33% and 3.33% had Grade II and Grade III neutropenia, respectively. In the weekly arm, number of patients having Grade II and Grade III neutropenia were 13.33% and 3.33%, respectively. Two meta-analyses comparing concurrent weekly cisplatin to tri-weekly cisplatin-based CTRT for treatment of cervical cancer suggested the superiority of the weekly cisplatin regimen based on the lower incidence of hematological toxicity.[13,14]

Although baseline mean serum urea and creatinine levels were comparable in both arms weekly comparison revealed a statistically not significant trend toward increase in mean serum urea and creatinine level in the tri-weekly arm as the treatment progressed. Two (6.67%) patients in the study arm and 4(13.33%) patients in the control arm had nephrotoxicity of Grade II or more, though this was statistically not significant (P=0.654). Hence, it can be concluded that as per nephrotoxicity was concerned, they were comparable between two treatment arms.

Total mean treatment duration in study arm was 68 days, and in control arm, it was 68.4 days. Total 50% of all patients required treatment interruption during treatment due to Grade III or above acute toxicities. Numerically, weekly cisplatin arm had higher incidence of treatment interruption than tri-weekly cisplatin arm (53.3% vs. 46.6%, P=0.517). Higher incidence of treatment interruptions in control arm may also be due to lack of compliance of patients in taking concurrent chemotherapy every week. Our findings with respect to treatment compliance were consistent with that of Einstein et al.[15]

Limitations of the study

This study has its limitations also-first, our sample size was small, so any statistical data have to be interpreted with caution. Second, it was a single institutional study; hence, results derived cannot be extrapolated on entire population and entire study duration was almost 18 months including patient accrual, intervention, and assessment. Hence, the late toxicity profile, disease-free survival/progression-free survival, overall survival, and late toxicities can't be assessed appropriately.

CONCLUSION

Hence, it can be stated that tri-weekly cisplatin-based concurrent chemoradiation is equally effective in controlling the disease with comparable acute toxicity. Therefore, tri-weekly cisplatin-based concurrent chemoradiation can be used as an acceptable alternative to standard weekly cisplatin-based concurrent chemoradiation in patients of locally advanced squamous cell cancer cervix. Further studies with higher number of patients and longer follow-up may be needed to establish these observations.

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AM- Concept and design of the study, preparation of the first draft of manuscript; **SS**- Data collection and statistical analysis, reviewed the manuscript; **KB-** Concept and Co-ordination, prepared the manuscript; **LB**- Literature review, interpretation of results, reviewed the manuscript; **SM**- did the literature review, intellectual contribution and final editing of the manuscript.

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