

# Phase IIb trial comparing two concurrent cisplatin schedules in locally advanced head and neck cancer

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## Abstract

**Background:** Concurrent chemoradiation with 3 weekly cisplatin (100 mg/m<sup>2</sup>) is the standard of care for locally advanced head and neck cancer. However, this regimen has been shown to be associated with lesser compliance and higher toxicities. Hence, there is a need to explore alternative concurrent cisplatin regimens. **Objectives:** The objective of this study was to compare the efficacy and toxicities of 3 weekly cisplatin (100 mg/m<sup>2</sup>) with weekly cisplatin (40 mg/m<sup>2</sup>) concurrently with radiation in patients with locally advanced head and neck cancer. **Patients and Methods:** This phase IIb trial randomized 56 patients with Stage III and IV squamous cell carcinoma of oropharynx, hypopharynx, and larynx to Arm A or Arm B. Arm A received cisplatin 100 mg/m<sup>2</sup> 3 weekly and Arm B received cisplatin 40 mg/m<sup>2</sup> weekly concurrently with radiation. The primary end point was disease-free survival (DFS) and secondary end points were overall survival (OS) and acute toxicity. DFS and OS were estimated using Kaplan–Meier method, and log-rank test was used to assess the difference in these distributions with respect to treatment. **Results:** The 2-year DFS in Arm A and Arm B was 64.5% and 52.8%, respectively ( $P = 0.67$ ). The OS at 2 years was 71% and 61.1% in Arm A and Arm B, respectively ( $P = 0.61$ ). There were no significant differences in acute hematological, renal, or mucosal toxicities between the two arms. **Conclusion:** This study showed a nonsignificant improvement in DFS and OS in the 3 weekly cisplatin arm over the weekly arm with comparable toxicities. The trial is registered with Clinical Trial Registry of India (CTRI registration number: CTRI/2013/05/003703, URL-<http://ctri.nic.in>).

**Key words:** Chemoradiation, cisplatin, head and neck cancer

## Introduction

Head and neck cancer is the fifth most common cancer worldwide.<sup>[1]</sup> About 60% of head and neck squamous cell carcinomas are diagnosed at advanced stage.<sup>[2]</sup> Concurrent chemoradiation is the standard nonsurgical treatment for locally advanced head and neck squamous cell carcinoma.<sup>[3,4]</sup> Although several clinical trials including the Meta-analyses of chemotherapy in head and neck cancer have demonstrated survival benefit from chemo-radiotherapy,<sup>[5]</sup> the optimal concurrent regimen has not yet been defined. Although cisplatin at the dose of 100 mg/m<sup>2</sup> on days 1, 22, and 43 is considered the preferred regimen,<sup>[6,7]</sup> it is associated with lesser compliance<sup>[8]</sup> and higher toxicity.<sup>[9]</sup> Attempts to reduce the toxicities of cisplatin have been made by reducing the total cumulative dose and fractionating the chemotherapy regimen. Alternative cisplatin dosing schedules such as 30–40 mg/m<sup>2</sup> weekly,<sup>[10,11]</sup> 6 mg/m<sup>2</sup> daily,<sup>[12]</sup> and 20 mg/m<sup>2</sup> daily for 5 days on weeks 1 and 5<sup>[13]</sup> have been tried to improve patient tolerance. Weekly dosing of cisplatin could allow adapting the intensity of treatment to the individual tolerance, thereby avoiding radiotherapy interruptions.

Several retrospective studies with concurrent weekly cisplatin have shown varying results on survival outcomes and toxicities.<sup>[14–19]</sup> At present, there is no prospective randomized data comparing weekly and 3 weekly cisplatin in the definitive chemoradiation setting. This prospective randomized trial was conducted to compare the efficacy and toxicity of 3 weekly cisplatin at 100 mg/m<sup>2</sup> with weekly cisplatin at 40 mg/m<sup>2</sup> concurrently with radiation in locally advanced head and neck squamous cell carcinoma.

## Patients and Methods

This randomized phase IIb trial was conducted at Regional Cancer Centre, Trivandrum, Kerala, India, from June 2013

to May 2014. This study was approved by the Institutional Review Board (IRB-01-2013/10) and the Ethics Committee (HEC No-05/2010). The trial is registered with Clinical Trial Registry of India (CTRI no: CTRI/2013/05/003703).

## Eligibility criteria

Patients who met all the following criteria were included in the study: (1) Previously untreated patients with stage III and IV squamous cell carcinoma of oropharynx, hypopharynx, and larynx, (2) age in the range of 18–70 years, (3) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, (4) baseline hemoglobin  $\geq 10$  g/dl, white blood cells count  $\geq 4000$  cells per cubic millimeter, platelet count  $\geq 100,000$  cells per cubic millimeter, and (5) creatinine clearance of  $\geq 60$  ml/min. The creatinine clearance was determined from 24 h urine sample and serum creatinine value. Patients with bone or cartilage involvement and with distant metastasis were excluded from the study.

## Study design

Out of the 78 patients screened, 56 were eligible for randomization. Patients were randomized into either Arm A or Arm B using a computer-generated randomization chart. Patients in Arm A received cisplatin 100 mg/m<sup>2</sup> 3 weekly and patients in Arm B received cisplatin 40 mg/m<sup>2</sup> weekly concurrently with radiation. All patients received radical radiotherapy, 66 Gy in 33 fractions over 6.5 weeks.

## Treatment

Patients were immobilized using head and neck thermoplastic cast and were treated with conventional technique. Primary and upper neck was treated with lateral parallel-opposed pair with multileaf collimator-shaped fields and the lower neck was treated using anterior field. All patients were treated with 6 MV photons using conventional fractionation, 200 cGy per fraction,

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**How to cite this article:** Nair LM, Kumar RR, Thomachan KC, Rafi M, George PS, Krishna KM, *et al.* Phase IIb trial comparing two concurrent cisplatin schedules in locally advanced head and neck cancer. *South Asian J Cancer* 2017;6:64–8.

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DOI: 10.4103/2278-330X.208840

one fraction per day, 5 days/week. The gross tumor received a dose of 66 Gy in 33 fractions over 6.5 weeks. Involved neck nodes were treated to 60–66 Gy in 30–33 fractions whereas uninvolved neck received 50 Gy in 25 fractions. Spinal cord shielding was given after 40 Gy. Posterior neck was treated with electron boost, delivering 60–66 Gy to involved nodal areas and 50 Gy to uninvolved nodes.

Cisplatin was administered concurrently with radiation either weekly or 3 weekly according to the randomization. For 3 weekly cisplatin, 1000 ml normal saline (NS) with 20 mmol potassium chloride (KCl) and 10 mmol magnesium sulfate ( $MgSO_4$ ) followed by 200 ml 10% mannitol were given as prehydration. This was followed by cisplatin 100 mg/m<sup>2</sup> in 1000 ml NS. Posthydration consisted of 1000 ml NS with 20 mmol KCl and 10 mmol  $MgSO_4$ . For 40 mg/m<sup>2</sup> cisplatin, 500 ml NS and 200 ml 10% mannitol were given as prehydration followed by cisplatin in 1000 ml NS. Posthydration consisted of 500 ml oral fluids.

Antiemetic prophylaxis consisted of 8 mg ondansetron, 12 mg dexamethasone as intravenous bolus, and NK1 antagonist 125 mg orally on the day of chemotherapy. Dexamethasone 8 mg per day and NK1 antagonist 80 mg were continued on the second and third days after each cycle. The entire treatment was administered on an outpatient basis.

#### Dose modification

Cisplatin was delayed until absolute neutrophil count (ANC) reached 1500/cu mm and platelet count reached 100,000/cu mm. If the ANC or platelet count remained below the above cutoff values on two occasions taken 2 days apart, that cycle of chemotherapy was omitted. Cisplatin dose was modified to 75% in cases of creatinine clearance value between 45 and 59 ml/min. 50% dose reduction was given for creatinine clearance values between 30 and 45 ml/min, and cisplatin was omitted for creatinine clearance below 30 ml/min.

#### Toxicity assessment during treatment

All patients were monitored weekly during the course of chemoradiation for the assessment of mucositis, dermatitis, dysphagia, vomiting, hematological parameters, renal function tests, and body weight. Radiotherapy toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) grading, and chemotherapy toxicities were graded according to the Common Toxicity Criteria-Adverse Events version 4.

#### Assessment of response

After completion of treatment, the first follow-up was done at 1 month and subsequently the follow-up was done at three monthly intervals. Response was assessed at 3 months of completion of treatment. Clinical examination and endoscopic evaluation were done for all patients. Those patients with clinical complete response were not subjected to further imaging. Patients with residual disease were considered nonresponders and their response was assessed using the RECIST criteria.

#### Statistical analysis

The primary end point was disease-free survival (DFS). The secondary end points were overall survival (OS) and acute toxicity. Since this was designed to be a phase II study and due to the paucity of similar studies, no predetermined sample size was calculated. It was decided to randomize 100 patients

from June 2013 to May 2014. However, only 56 patients could be accrued during this study period. DFS was calculated from the date of randomization to the date of recurrence or death. OS was calculated from the date of randomization to the date of death or last follow-up. Kaplan–Meier method was used to estimate OS and DFS, and the log-rank test was used to assess differences in these distributions with respect to treatment. The difference in cisplatin dose intensity in Arm A and Arm B was analyzed using Chi-square test. Chi-square test and Fisher's exact test were employed to test the proportions of acute toxicity differences. All tests were two-sided, and  $P < 0.05$  was considered statistically significant.

## Results

From June 2013 to May 2014, 56 patients were randomized. Thirty-one patients were in the control arm of 3 weekly cisplatin 100 mg/m<sup>2</sup> (Arm A) and 25 patients in the study arm of weekly cisplatin 40 mg/m<sup>2</sup> (Arm B). These patients were followed up till November 31, 2015. Median follow-up of the surviving patients was 26 months. One patient in the weekly arm did not complete the treatment and was excluded from the analysis. Fifty-five patients were eligible for the final analysis. The study design is shown in Figure 1. Baseline patient characteristics were evenly distributed across both groups as shown in Table 1.

#### Compliance to treatment

Median duration of treatment was 45 days (40–63 days). Two patients in the Arm A and one patient in the Arm B had radiation interruption for more than 5 days. All patients completed radiation except one who died before the completion of treatment. Of the 31 patients in the Arm A, only 11 patients (35%) received the planned three cycles of chemotherapy and 65% received two cycles. The reasons for chemotherapy omission were neutropenia (seven), anemia and neutropenia (four), renal dysfunction (four), neutropenia and thrombocytopenia (one), and ECOG performance status  $\geq 2$  (three). In Arm B, 62.5% of the patients received all the six cycles and 33% of the patients received five cycles of chemotherapy. In the weekly arm, the reasons for chemotherapy omissions were neutropenia (three), renal dysfunction (two), neutropenia and thrombocytopenia (one), anemia and neutropenia (one), and neutropenia and renal dysfunction (two). The mean dose of cisplatin in 3 weekly arm was 356.6 mg and 339.1 mg in the weekly arm [Table 2]. Six patients were hospitalized during chemoradiation. The reasons for admission are hyponatremia (three), renal dysfunction (one), vomiting (one), and oral mucositis leading to poor oral intake (one).

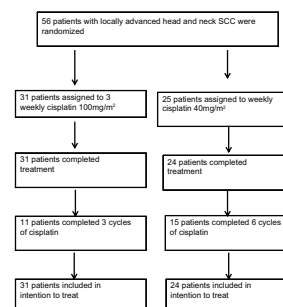


Figure 1: The trial design

**Response to treatment**

Nearly 90.3% of the patients in the 3 weekly arm and 75% of the patients in the weekly arm attained complete response at 6 months of completion of treatment. The partial response rates were 6.4% and 12%, respectively. One patient in 3 weekly arm and three patients in the weekly arm died before the first follow-up. Four patients had residual disease at 12 weeks after treatment, two in each arm. None of them were amenable to salvage surgery. Four patients in Arm A developed local recurrence, one patient had salvage surgery (total laryngectomy and neck dissection), and others were treated with palliative chemotherapy. In Arm B, two patients developed local recurrence and one patient developed lung metastasis. The mean time to relapse was 15.16 months (16.01 months in the 3 weekly arm and 14.31 months in the weekly arm). Two patients developed second primary in esophagus, one in each arm. One patient in Arm B developed second primary in tongue and was treated with wide excision and neck dissection. Locoregional control at 2 years was 61.3% in the 3 weekly arm and 62.5% in the weekly cisplatin arm. The 2-year DFS in Arm A and Arm B was 64.5% and 52.8%, respectively ( $P = 0.674$ ) [Figure 2]. There was a nonsignificant improvement in 2-year OS in Arm A compared to Arm B (71% vs. 61.1%,  $P = 0.610$ ) [Figure 3].

Of the 19 deaths, 8 patients died due to disease, 4 deaths were treatment related (death of unknown cause <2 months of treatment completion), 2 patients died due to cardiac events (both events occurred 1 year after treatment), and the cause of death was not known in 5 patients.

**Table 1: Baseline patient characteristics**

Characteristic	Arm A (n=31)	Arm B (n=24)	P
Age			
≤60	17 (54.83)	14 (45.16)	0.999
>60	14 (45.16)	10 (41.66)	
Sex			
Male	28 (90.3)	23 (95.83)	0.623
Female	3 (9.67)	1 (4.16)	
Performance status			
0	14 (45.16)	12 (50)	0.78
1	17 (54.83)	12 (50)	
Site			
Oropharynx	17 (54.83)	10 (41.66)	0.31
Hypopharynx	7 (22.58)	4 (16.66)	
Larynx	7 (22.58)	10 (41.66)	
T stage			
T2	11 (35.48)	5 (20.83)	0.30
T3	17 (54.83)	14 (58.33)	
T4	3 (9.67)	5 (20.83)	
N stage			
N0	7 (22.5)	7 (29.16)	0.73
N1	12 (38.70)	7 (29.16)	
N2	12 (38.70)	10 (41.66)	
AJCC stage			
III	18 (58.04)	15 (62.5)	0.78
IV	13 (41.93)	9 (37.5)	

AJCC=American Joint Committee on Cancer

**Table 2: Cumulative dose of cisplatin in each group**

Cisplatin dose (mg/m <sup>2</sup> )	Arm A (%)	Arm B (%)	P
≤200	20 (64.5)	9 (37.5)	0.08
>200	11 (35.48)	15 (62.5)	

**Toxicities**

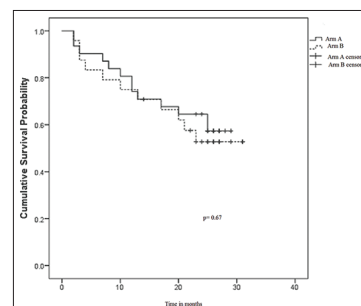
Acute toxic effects are listed in Table 3. There were no significant differences in acute hematological, renal, or mucosal toxicities between the two groups. There were no Grade 4 mucosal or hematological toxicities. Two patients in Arm A developed Grade 2 vomiting. Mean reduction in the weight from prechemotherapy baseline was 5.8 kg in the 3 weekly arm and 6.04 kg in the weekly arm.

**Discussion**

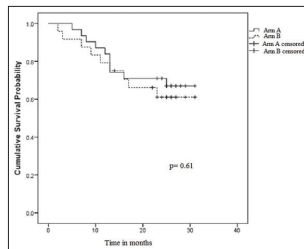
Concurrent chemoradiation with cisplatin 100 mg/m<sup>2</sup> 3 weekly is the standard of care for locally advanced head and neck cancer.<sup>[3,4]</sup> However, this regimen is associated with higher toxicities, and the compliance to treatment is poor. In a phase III trial involving patients with carcinoma nasopharynx, only 63% of patients in the chemoradiation arm with cisplatin 100 mg/m<sup>2</sup> 3 weekly completed all the three cycles of chemotherapy.<sup>[20]</sup> Low-dose cisplatin was tried in many trials to increase the compliance and to decrease the toxicities.<sup>[21,22]</sup> In a randomized phase III trial comparing radiotherapy and chemoradiation with cisplatin 20 mg/m<sup>2</sup> weekly,<sup>[21]</sup> there was no significant difference between the two groups. Concomitant daily cisplatin 4 mg/m<sup>2</sup> was also found to be suboptimal to other high-dose regimens.<sup>[22]</sup> Concurrent chemoradiation with weekly cisplatin 40 mg/m<sup>2</sup> was tested in advanced nasopharyngeal cancer and was found to have prolonged progression-free survival compared to RT alone arm.<sup>[11]</sup> There are many retrospective studies comparing concurrent weekly and 3 weekly cisplatin in the definitive chemoradiation setting, but none has been conclusive yet.<sup>[15-19]</sup> Data from prospective studies are not available. This study was done prospectively to compare the efficacy and toxicities of the two cisplatin regimens concurrently with radiation.

In the dose-intensity comparison by Ho *et al.*, concurrent cisplatin 100 mg/m<sup>2</sup> 3 weekly was less tolerated than weekly cisplatin 40 mg/m<sup>2</sup> and more patients were able to receive a higher cumulative dose of >200 mg/m<sup>2</sup> with the weekly schedule.<sup>[15]</sup> In the present study also, more patients in weekly arm attained cumulative dose of cisplatin >200 mg/m<sup>2</sup>, but the mean dose of cisplatin was comparable in both the arms. In the study by Ho *et al.*, 41% of patients in the weekly arm received 6 cycles and no patient in the 3 weekly arm completed the full three courses of chemotherapy. In this study, 35% of patients in 3 weekly arm completed all the three cycles and 62.5% of patients in the weekly arm received all the six cycles of chemotherapy.

In the retrospective analysis by Ho *et al.*, 3 weekly cisplatin regimen had more Grade 3 radiation dermatitis, but the difference was not significant. In another retrospective study by



**Figure 2: Kaplan–Meier estimate of disease-free survival according to two cisplatin schedules**



**Figure 3: Kaplan-Meier estimate of overall survival according to two cisplatin schedules**

**Table 3: Acute toxicities**

Toxicity	Arm A (n=31)	Arm B (n=24)	P
Mucositis			
Any grade	30 (96.7)	23 (95.83)	0.900
Grade 3/4	16 (51.6)	13 (54.1)	
Dysphagia			
Any grade	29 (93.5)	23 (95.83)	0.153
Grade 3/4	8 (25.8)	15 (62.5)	
Dermatitis			
Any grade (%)	31 (100)	24 (100)	0.486
Grade 3/4	1 (3.2)	3 (12.5)	
Anemia			
Any grade	7 (22.5)	2 (8.3)	0.300
Grade 3/4	0	1 (4.1)	
Neutropenia			
Any grade	14 (45.16)	11 (45.83)	0.583
Grade 3/4	1 (3.2)	2 (8.3)	
Thrombocytopenia			
Grade 1	1 (3.2)	1 (4.1)	0.999
Grade 2	0	1 (4.1)	
Renal toxicity			
Grade 1	2 (6.45)	4 (16.6)	0.428
Grade 2	1 (3.2)	0	

Geeta *et al.*, weekly cisplatin schedule had higher rate of severe mucositis, dermatitis, and hematological toxicities.<sup>[16]</sup> Uygun *et al.* reported Grade 3 and 4 toxicities in 53.3% of patients in the 3 weekly arm and 40% of patients in the weekly arm.<sup>[17]</sup> The present study did not show any significant difference in hematological, mucosal, or skin toxicities between the two arms.

Ho *et al.* reported OS rate of 52% in the 3 weekly arm compared to 71% in the weekly arm at a median follow-up of 26 months.<sup>[15]</sup> Kose *et al.* reported 2-year OS rates of 56% and 63% in 3 weekly and weekly arms, respectively, without any difference in toxicities.<sup>[18]</sup> In another retrospective study, Espeli *et al.* reported better OS rate in 3 weekly cisplatin with intensity modulated radiation therapy (IMRT) group compared to weekly cisplatin with IMRT group, with comparable progression-free survival.<sup>[19]</sup> The present study showed 2-year DFS rates of 64.5% and 52.8% in 3 weekly and weekly cisplatin arms, respectively ( $P = 0.674$ ). Two-year OS was 71% in 3 weekly arm and 61.1% in the weekly arm ( $P = 0.610$ ). Even though majority of patients in the 3 weekly arm received only 2 cycles of concurrent cisplatin, a nonsignificant improvement in DFS and OS was observed with the 3 weekly schedule. Information on the optimal number of concurrent chemotherapy cycles to be given is still not clear.

This study has few limitations. Sample size was small and was not powered enough to find any significant difference

in outcome between the two groups. Follow-up is short to comment on the survival outcomes. Chronic toxicities were not evaluated, and quality of life analysis was not done between the arms.

## Conclusion

The present study showed a nonsignificant improvement in DFS and OS in the 3 weekly cisplatin arm compared to the weekly cisplatin arm with comparable toxicities, though majority of patients in the 3 weekly arm received only two cycles of concurrent cisplatin. Large phase III studies would be required to arrive at a conclusion on the optimal dose and cycles of concurrent cisplatin in head and neck cancer.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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