Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

A Prospective Randomized Comparison of Concurrent Chemoradiotherapy Using Weekly Versus Three Weekly Cisplatin in Head and Neck Carcinoma

Bidisha Naskar Ghosh[1], Harris Mahammad Sepai[2], Pratyusha Mukherjee[2]

[1]Associate Professor, Department of Radiotherapy, IPGME&R, Kolkata, India.

[2]RMO-cum-Clinical Tutor, Department of Radiotherapy, IPGME&R, Kolkata, India.

Received: January 2021
Accepted: February 2021

ABSTRACT

Background: Head and Neck Cancers constitute around 30% of cancers occurring in India and most cases present with locally advanced disease. Concurrent chemoradiotherapy with cisplatin is the standard treatment for these cases. The standard regimen includes three-weekly cisplatin, but weekly regimens are often used to due to ease of administration and clinical impression of reduced toxicity. Our study aims at comparing response and acute toxicity between these two regimens. **Methods:** Sixty patients of locally advanced Squamous Cell Carcinoma of head and neck were randomized into two arms: Arm A (n=30) patients received injection cisplatin 40 mg/m2 weekly along with radiation; Arm B (n=30) patients received injection cisplatin 100 mg/m2 three-weekly along with radiation. Radiotherapy was delivered to a total dose of 66 Gy in conventional fractionation. **Results:** In arm A complete response was 60% and partial response was 26.67%; whereas in arm B complete response was 73.33% and partial response was 20%, which was not statistically significant. In analyzing response rate site wise, for oropharyngeal carcinoma, there was a trend of improved response favouring 3-weekly arm (B) (p= 0.065). Major toxicities included mucositis, dermatitis, vomiting, neutropenia, anaemia and acute xerostomia. Incidence of acute toxicity is similar in both the arms. **Conclusions:** We conclude in this study that weekly cisplatin despite having logistic and theoretical advantage in comparision to three weekly cisplatin, a trend of superior efficacy in the three weekly cisplatin arm with similar acute toxicity profile justifies use of three weekly cisplatin as the standard of care.

Keywords: Head and Neck cancer, Chemoradiation, Cisplatin.

1

INTRODUCTION

Head and neck cancer comprises a huge burden of disease worldwide. It is the fifth most common malignancy globally among adults.[1] It is amongst the commonest malignancy in India. Overall 57.5% of global head and neck cancer occur in Asia especially in India.[2] Most randomized clinical trials show the superiority of combined RT and chemotherapy to RT alone for the treatment of locally advanced, nonmetastatic Head and Neck Cancer. A meta-analysis of individual patient data from >17,346 participants in 93 trials conducted from 1965 to 2000 (Meta-Analysis of Chemotherapy on Head and Neck Cancer [MACH-NC]) demonstrated that the use of radiotherapy and concurrent chemotherapy (CRT) resulted in a 19% reduction in the risk of death and an overall 6.5% improvement in 5-year survival compared to treatment with RT alone.[3] Currently CRT using cisplatin (100mg/m2) on day 1 and repeated every three weeks during radiotherapy is considered standard among different CRT protocols.[4] This schedule was originally developed for use in clinical trials of induction chemotherapy regimen and later incorporated in CRT regimen. This regimen is, however, usually associated with significant acute toxicities such as mucositis, hematological complication, and renal complication. Smaller individual doses of drug may lead to less chemotherapy-induced morbidity without compromise of efficacy.[5,6] Concurrent CRT using such schedules has proven very effective and become the standard of care in squamous carcinoma of the uterine cervix.[7-10]

Weekly cisplatin regimens have been increasingly used, in large part because of their relative ease of administration and the clinical impression of reduced toxicity. It is important to stress the limitations of this experience. No direct comparison has been made between the weekly and the every-three-week regimens. Therefore we would like to perform a prospective randomised study to compare locoregional control and toxicity of the weekly and three weekly cisplatin based CRT.

Name & Address of Corresponding Author
Dr. Harris Mahammad Sepai
North Mill, Radhanagar,
Bauria, Howrah-711310, WB, India
Email: harris.nrs@gmail.com

MATERIALS & METHODS

Histopathologically confirmed cases of locally advanced squamous cell carcinoma of oropharynx, hypopharynx and larynx with good performance status and normal complete blood count and hepatic

and renal function registered between February 2016 to December 2017 were included in the study. Patients not meeting above inclusion criteria were excluded from our study. Total sixty patients were included in our study.

Patients were randomly assigned in two different arms. Patients in Arm A received External Beam Radiotherapy (EBRT) with dose of 66 Gy in conventional fractionation along with Injection CISPLATIN (dose 40 mg/m2 weekly, for five weeks) and in Arm B patients received 66 Gy in 2 Gy/fraction in conventional fractionation along with Injection CISPLATIN (dose 100 mg/m2 at 3 week interval, for two cycles). Radiation was delivered in three phases using shrinking field technique. Chemotherapy with Inj. Cisplatin was administered with adequate prehydration and premedication.

Acute toxicities were assessed by weekly history taking, physical examination, study of blood parameters and weight during treatment and graded according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Patients were followed up at 6-8 weeks after completion of treatment based on detailed ENT examination and contrast enhanced CT scan of head and neck. Biopsy was taken any suspicious clinical and/or radiological residual disease of primary site and/or nodal area. Patients were then categorized as per RECIST Criteria as having complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Statistical Analysis was conducted using IBM SPSS Statistics version19.0 (SPSS Inc. Chicago, IL).

RESULTS

The mean age of the patients enrolled for the study was 59.23 Yrs with a minimum of 33 yrs to maximum 75 yrs. The male patients accounted for 83.3% patients and female patients accounted for 16.7% patients included in the study. Out of sixty patients 34 (56.7%) patients presented with oropharyngeal cancer, 8 (13.3%) patients presented with hypopharyngeal cancer and 18 (30%) patients presented with laryngeal cancer [Figure 1]. Out of sixty patients 24 (40%) patients presented with stage III disease, whereas 36 (60%) patients presented with stage IVA [Figure 2].

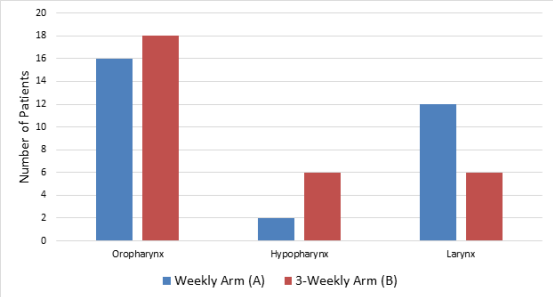

Figure 1: Distribution of Patients according to Sites

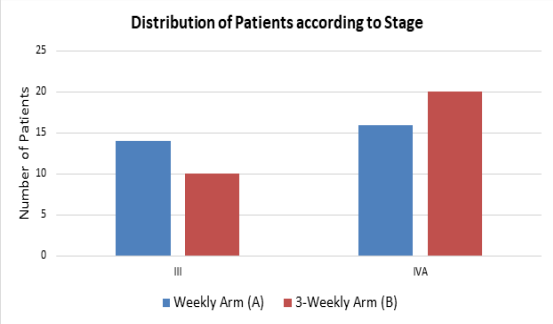

Figure 2: Distribution of Patients according to Stage

Table 1: Comparison of Treatment Response in between the two Arms

Response (RECIST)	ARM A		ARM B		P value
	n	%	n	%	
Complete response	18	60%	22	73.3%	0.443
Partial response	08	26.67%	06	20%	
Stable disease	02	6.67%	00	00	
Progressive disease	02	6.67%	02	6.67%	

Table 2: Response Assessment comparison according to Primary Site

Site	Response (RECIST)	ARM A		ARM B		P value
		n	%	n	%	
Oropharynx	Completeresponse	8		16		0.065
	Partial response	4		2		
	Stable disease	2		0		
	Progressivedisease	2		0		
Hypopharynx	Complete response	0		2		0.536
	Partial response	2		4		
	Stable disease	0		0		
	Progressivedisease	0		0		
Larynx	Complete response	10		4		0.076
	Partial response	2		0		
	Stable disease	0		0		
	Progressive disease	0		2		

The mean duration of treatment in all patients was 45.23 days with a standard deviation of approximately 2 days. The minimum time required to complete treatment was 42 days and maximum duration of treatment was 51 days.

In Arm A, complete response rate was 60% and partial response rate was 26.67%, i.e. overall response rate of 86.67%. In Arm B, complete response rate was 73.33% and partial response rate was 20% i.e. overall response rate 93.33% [Table 1].

However this difference in overall response in these two arms was not statistically significant (p=0.443). In analysing the response rate site wise, statistically significant difference was not observed for any site [Table 2]. However, for oropharyngeal carcinoma, there was a trend of improved response favouring 3-weekly arm (B) (p= 0.065). In weekly arm (A), there were 16 patients of oropharyngeal carcinoma, of which 8 patients have complete response, compared to 16 complete response in 3-weekly arm (B) containing 18 patients of oropharyngeal carcinoma.

Incidence of neutropenia was higher in weekly arm (A) in comparison to 3-weekly arm and it was found to be statistically significant (p= 0.042) [Table 3]. Although when we compare development of grade II or higher toxicity, statistical significance was not reached (p=0.125). In each arm, 4 patient experienced grade III neutropenia requiring myeloid growth factor (Filgrastim) support. In spite of using higher bolus dose of cisplatin per cycle in 3-weekly arm (B), acute nephrotoxicity incidence is similar in both arms. Grade II or higher incidence of weight loss were similar in both arms. But grade III weight loss (more than 20% weight loss from baseline) was observed in 4 patients of weekly arm (A), compared to none in 3-weekly arm (B). Incidence of acute xerostomia was significantly higher in patients treated with weekly cisplatin (p=0.015).

Table 3: Comparison of Grade II or higher acute toxicity in between the two Arms

Acute Toxicity	Grade II or higher toxicity		P Value
	Arm A	Arm B	
Anemia	8	12	0.412
Leucopenia	12	6	0.158
Neutropenia	10	14	0.125
Lymphocytopenia	20	22	0.779
Thrombocytopenia	2	0	0.492
Acute Nephrotoxicity	4	2	0.671
Weight Loss	16	16	1.00
Anorexia	8	2	0.080
Nausea	0	4	0.112
Vomiting	2	6	0.254
Dysphagia	24	26	0.731
Acute Xerostomia	16	6	0.015
Oral Mucositis	14	16	0.797
Oral Pain	8	14	0.180
Acute Dermatitis	12	6	0.158

DISCUSSION

Most randomized trials evaluating the role of concurrent cisplatin-based chemoradiotherapy used a three weekly schedule of cisplatin 100 mg/m2 and this treatment regimen is considered the standard therapy in locally advanced head and neck cancer patients. However, it is associated with substantial toxicity and many trials showed suboptimal compliance with cisplatin 100 mg/m2 potentially negatively influencing the outcome.[11] Therefore, low-dose weekly cisplatin schedules are frequently used in clinical practice despite the lack of evidence from prospective randomized trials.[12]

In our study both Arm A and Arm B received a total dose of 66 Gy in 33 fraction using conventional fractionation schedule. Concurrently Arm A received chemotherapy with injection Cisplatin (40 mg/m2) weekly starting from the Day1 of Radiotherapy for consecutive five cycles with a cumulative dose of 200 mg/m2. Whereas Arm B received chemotherapy with injection Cisplatin (100 mg/m2) at 3 week interval, starting on Day 1 of Radiotherapy for two cycles, with a cumulative dose of 200 mg/m2. So in terms of treatment received, both arms were very much comparable to each other except the more frequent chemotherapy schedule in Arm A. Many investigators consider 100 mg/m2 bolus dosing of CDDP on days 1, 22, and 43 of RT (with total cumulative dose of Cisplatin 300 mg/m2) to be standard. Compliance is a significant problem with the standard three-cycle concurrent CDDP paradigm. Nearly one-third of patients do not receive all cycles, and subset analyses suggest that two cycles are as effective as three.[13-15] RTOG 0129 and other studies have suggested that there may be a minimum cumulative threshold dose of approximately 200 mg/m2 of cisplatin that is required to achieve maximal benefit when used concomitantly with radiation.[16,17] Hence, in the present study, total cumulative dose of injection Cisplatin was 200 mg/m2.

In Arm A, complete response rate was 60% and partial response rate was 26.67%, i.e. overall response rate of 86.67%. In Arm B, complete response rate was 73.33% and partial response rate was 20% i.e. overall response rate 93.33%. However this difference in overall response in these two arms was not statistically significant (p=0.443). In analysing the response rate site wise, statistically significant difference was not observed for any site (Table). However, for oropharyngeal carcinoma, there was a trend of improved response favouring 3-weekly (arm B) (p= 0.065). A large randomized non-inferiority trial (N = 300) compared cisplatin 30 mg/m2 given once a week and cisplatin 100 mg/m2 given once every 3 weeks concurrently with curative intent RT was published.[18] The primary aim to show non-inferiority for the weekly regimen was not reached. In fact, locoregional tumor control was superior with the high-dose 3-weekly regimen. In our study we found incidence of acute toxicity is similar in both the arms, although there is statistically increased incidence of acute xerostomia in weekly arm. In spite of using higher bolus dose of cisplatin per cycle in 3-weekly (arm B), acute nephrotoxicity incidence is similar in both arms.

CONCLUSION

We conclude in this study that weekly cisplatin despite having logistic and theoretical advantage in comparision to three weekly cisplatin, a trend of superior efficacy in the three weekly cisplatin arm

with similar acute toxicity profile justifies use of three weekly cisplatin as the standard of care in concurrent chemoradiation in locally advanced squamous cell carcinoma of head and neck. However further studies with greater number of patients and longer duration of follow up is necessary to draw a definitive conclusion.

Compliance with ethical standards

Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975.

Informed consent taken from each patients before randomization.

REFERENCES

1. Jemal A, Murray T, Thomas A, Cancer statistics, 2005. CA cancer J Clin2003; 53: 5-26
2. Chaturvedi P. Head and neck surgery. J Can Res Ther 2009; 5:143
3. Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
4. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349: 2091-8.
5. Kurihara N, Kubota T, Hoshiya Y, Otani Y, Ando N, Kumai K, et al. Pharmacokinetics of cis-diamminedi-chloroplatinum (II) given as low-dose and high-dose infusions. J Surg Oncol 1996; 62: 135-138.
6. Nagai N, Ogata H. Quantitative relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity in rats: Importance of area under the concentration-time curve (AUC) as the major toxicodynamic determinant in vivo. Cancer Chemother Pharmacol 1997; 40: 11-18.
7. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18:1606–1613.
8. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999; 340:1137–1143.
9. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999; 340:1144–1153.
10. Thomas GM. Improved treatment for cervical cancer–concurrent chemotherapy and radiotherapy. N Engl J Med1999;340:1198–1200.
11. Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003;21:92–8.
12. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys. 1996;36:999–1004.
13. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091–2098.
14. Bensadoun RJ, Benezery K, Dassonville O, et al. French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: results at 2 years (FNCLCC-GORTEC). Int J Radiat Oncol Biol Phys 2006;64:983–994.
15. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–1952.
16. Loong HH, Ma B, Mo F, et al. The effect of cisplatin dose administered during concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2011;29:abstr 5532.
17. 122. Ghi MG, Paccagnell A, Floriani I, et al. Concomitant chemoradiation in locally advanced head and neck squamous cell carcinoma: a literature-based meta-analysis on the platinum concomitant chemotherapy. J Clin Oncol 2011;29:abstr 5534.
18. Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-week versus once-Every-3-weeks cisplatin Chemoradiation for locally advanced head and neck Cancer: a phase III randomized noninferiority trial. J Clin Oncol. 2018;36:1064–72.

How to cite this article: Ghosh BN, Sepai HM, Mukherjee P. A Prospective Randomized Comparison of Concurrent Chemoradiotherapy Using Weekly Versus Three Weekly Cisplatin in Head and Neck Carcinoma. Ann. Int. Med. Den. Res. 2021; 7(2):RD14-RD17.

Source of Support: Nil, **Conflict of Interest:** None declared