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Research Article

A COMPARATIVE STUDY OF WEEKLY VERSUS THREE-WEEKLY CISPLATIN CONCURRENTLY WITH 3- DIMENSIONAL CONFORMAL RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCER

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A B S T R A C T

Introduction: Cisplatin based concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced head and neck squamous cell cancer (LAHNSCC) (stage III–IV), in a definitive radical upfront setting or after surgical resection in high-risk patients.Despite the routine use of 100 mg/m^2 cisplatin 3-weekly, the optimal dose and timing of cisplatin administration in various chemotherapy protocols have not been elucidated and available data is insufficient to suggest which chemotherapy schedule is superior in terms of better disease control.

Aim: To evaluate the efficacy and toxicity of weekly verses three weekly cisplatin given concurrently with radiotherapy in patients with LAHNSCC.

Materials and Methods: It was aprospectively randomized, two- arm comparative study included 110 LAHNSCC patients, which was randomized into two arms: Study arm (n=55) patients received cisplatin 30 mg/m^2 weekly for 6 weeks along with radiation; Control arm (n=55) patients received cisplatin three weekly 80 mg/m^2 on day 1, 22 and43 of radiation. Radiotherapy was delivered to a total dose of 70 Gy by 3-dimensional conformal technique at linear accelerator. Tumor response and toxicities were evaluated by the help of Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) criteria and Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Criteria respectively.

Results: complete response (CR) was achieved in 36 patients (65.5%) in the Study group and 35 patients (63.6%) in the Control group. The partial response (PR) rates were 15 patients (27.3%) in Study group and 13 patients (23.6%) in Control group. Mainly observed toxicities were mucositis, dermatitis, Nausea & vomiting, neutropenia, thrombocytopenia and nephrotoxicity. All observed toxicities were more in control group but the difference was statistically significant only for mucositis and nausea & vomiting

Conclusion: Weekly cisplatin is a well-tolerated schedule with concurrent radiotherapy without potentiating toxicities and having almost similar efficacy as that of three-weekly schedule.

INTRODUCTION

According to Globocan-2018 data the most commonly encountered malignancy in Indian population was of the Head and Neck region which constitutes about 16% among all. [1] Generally more than two- third cases of head and neck cancer are presented with loco-regionally advanced disease. While treating such advanced cases with external beam radiation alone, it causes poor results in terms of cure, loco-regional recurrence and overall survival.[2] Previous data reported the benefit of adding Chemotherapy (CT) to Radiotherapy (RT) for Loco-Regionally Advanced Head and Neck Squamous Cell Carcinomas (LAHNSCC). [3,4] MACH-NC meta-analysis by *Pignon et al*., [5] evaluated locoregional treatment with or without chemotherapy, and found the absolute 5-year survival benefit of 6.5% by adding chemotherapy. Another meta-analysis of randomized trials by *Budach et al*., [6] concluded that concurrent chemotherapy prolonged the survival by an average of 12 months but the sequential chemotherapy cannot. Concurrent chemoradiotherapy (CCRT) is the standard treatment for LAHNSCC (stage III–IV), in a definitive radical upfront setting or after surgical resection in high-risk patients. [7]

Cisplatin is the most commonly used and most effective one chemotherapeutic agent for CCRT due to its synergistic interaction and non-overlapping toxicities with radiotherapy. [8] Cisplatin is an alkylating chemotherapeutic agent which is highly emetogenic, myelosuppressive, nephrotoxic and ototoxic. Cisplatin administered at a dose of 100 mg/m^2 every 3 weeks on days 1, 22 and 43 with concurrent standard fractionated radiation therapy is the most commonly used due to highest evidence of clinical benefits. However, only 50% to

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60% of patients were able to receive complete 3 planned cycles of 100mg/m^2 cisplatin, because of poor tolerability and severe adverse effects.[5,9,10]In order to improve the treatment tolerability and reduce the acute toxicities with these high dose schedule, alternative schedules including weekly 40 mg/m^2, 20 mg/m^2 for 5 days three weekly and daily 6 mg/m^2 low-dose cisplatin have been used. [11-15]

In some institutes three weekly high-dose schedule has been gradually replaced by weekly low-dose cisplatin regimens because of some theoretical assumptions. Weekly low-dosecisplatin compared with high-dose three weekly cisplatin have some theoretical superiorities like: enhancing radio-sensitivity of tumor tissue [16], increase treatment compliance with avoidance of unscheduled interruptions in radiotherapy [17], reduce chemotherapy related acute and late toxicities without affecting its efficacy [16], easy to deliver the therapy on outpatient basis with overall cost benefits [18].

Despite the routine use of 100 mg/m^2 cisplatin 3-weekly, the optimal dose and timing of cisplatin administration in various chemotherapy protocols have not been elucidated and there is insufficient data to suggest which chemotherapy schedule is superior in terms of better disease control.

So, aim of this prospective analysis was to evaluate the efficacy and toxicity of weekly verses three weekly cisplatin given concurrently with radiotherapy in patients with LAHNSCC at our centre.

MATERIAL AND METHODS

It was a hospital based prospectively randomized, two- arm comparative study which was conducted in year 2016-2017 at a tertiary care centre of north- west India. After approval of institutional Review Board/ Ethical committee, histopathological proven LAHNSCC (stage III to IVB) patents, which were inoperable and treated with definitive chemoradiotherapy, and ready to give informed written consent, were included in this study. Patients of histopathology other than squamous, ECOG performance status 3 and 4, or previously treated with either surgery or chemo-radiotherapy were excluded from the study. Sample size was calculated at 80% study power & alpha error of 0.05, assuming grade 3 skin toxicity (radiation dermatitis) of 26% in weekly cisplatin group patients, while 56% in three- weekly cisplatin group patients as found in reference study by *Ho KF et al.*[19] Following above assumption 48 patients in each group were required as sample size which is enhanced to 55 patients in each group expecting 10% drop out/ lost to follow up/ attrition as final sample size.

All 110 eligible patients were treated with definitive CCRT. Radiotherapy was delivered to all patients with conformal 3 - dimension technique (3-DCRT) by linear accelerator to a total dose of 70 Gray in 35 fractions in 7 weeks. For concurrent chemotherapy all the patients were randomized in two groups (Group A and B) by chit-box method with replacement till the completion of required sample size. Group A was the study arm in which weekly cisplatin 30 mg/m^2 delivered for 6 weeks with 3-DCRT. In control group (group B) cisplatin was given three-weekly at 80 mg/m^2 on day 1, 22 and43 of 3-DCRT.

All patients were examined once weekly during the treatment. CBC and biochemical investigation were done and noted every time before the scheduled 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 be noted and necessary gap correction for radiotherapy dose was done accordingly. Chemotherapy was withheld during radiotherapy interruptions. Radiotherapy was planned to be continued in spite of chemotherapy being discontinued due to chemotherapy related toxicities.

Patient were completed the whole scheduled radiotherapy irrespective of the delay and received minimum 5 cycles of weekly cisplatin and minimum 2 cycles of three- weekly cisplatin chemotherapy.

The results of study group were analyzed & compared with control group in terms of tumor response and toxicities. Tumor response was evaluated at the time of treatment completion, 3 months and 6 months thereafter based on clinical examination and contrast enhanced CT scan of head and neck findings in each of the patient and categorized as per the Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1).[20]Toxicities were assessed and scored according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Criteria [21] in both the groups on weekly basis during the treatment and thereafter at 6 weeks, 3 months and 6 months. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumor at primary site and or nodal area. Collected data were analyzed by using Chi-square test for correlation.

RESULTS

In this prospective study total 110 LAHNSCC patients (55 in each group) were enrolled. In the Study Group, 52 patients were males and 3 were females and in the Control Group, 49 patients were males and 6 were females. The age of patients ranged between 21 – 70 years. The mean age in the study group is 53.96 years & in the control group is 53.5 years. The patients' clinical and demographic characteristics are summarized in Table 1. Both the groups were equally distributed and comparable in terms of age, gender, ECOG performance status, clinical stage, and localization of primary site without any significant difference. The most common histopathology was moderately differentiated squamous cell carcinoma (MDSCC), with 32 patients in the Study Group and 27 patients in the Control Group. 2 patients had ECOG performance status 0 (14 in the study group and 18 in the control group) 64 patients had ECOG performance status 1 (34 in the study group and 30 in the control group) and 14 patients had ECOG performance status 2 (7 in each group).

Most common site of primary tumour is oropharynx with 30 patients (55%) in the study group and 26 patients (47%) in the control group. According to the AJCC TNM Staging, 9 patients had T1, 13 patients had T2, 11 patients had T3 and 22 patient had T4 in the Study Group; and 8 patients had T1, 13 patients had T2, 14 patients had T3 and 20 patients had T4 in the Control group. The nodal status showed that 4 patients had N0, 9 patients had N1, 36 patients had N2, 6 patients had N3 in the Study Group; and 6 patients had N0, 11 patients had N1, 31 patients had N2 and 7 patients had N3 in the Control Group. The clinical response rates obtained after 6 months of treatment follow-up was demonstrated in Table-2 and revealed that complete response (CR) was achieved in 36 patients (65.5%) in the Study group and 35 patients (63.6%) in the Control group. The partial response (PR) rates were 15 patients (27.3%) in Study group and 13 patients (23.6%) in Control

group. Overall response (OR) rate (CR + PR) was 92.8% in the Study group and 87.2% in the Control group. Both CR and OR rates were found to be statistically not significant (p = 0.79). Two patients in the Study group developed progressive disease (PD) after completion of radiotherapy, whereas two patients in the Study group had Stable disease (SD). In the control group four patients had Progressive disease (PD) and three patients had Stable disease during the 6 months follow up period.

Observed toxicities of treatment were displayed in Table -3. The chief adverse effect both in the Study group and the Control group was acute oral mucositis. The incidence of grade 4 mucositis was more in the Control group i.e. 3 patients, compared to 2 patients in the Study group. Also, the incidence of grade 3 mucositis was more in the Control group with 36 patients, compared to 22 patients in the Study group which was statistically significant (p = 0.015). Most of the patients developing grade 3 or 4 mucositis needed dietary modification in the form of liquid diet, and those developing severe mucositis were managed with intravenous fluids, steroids and analgesics.

The incidence of grade 1 acute dermatitis was seen in 31 patients in Study group and 27 in the Control group; grade 2 dermatitis was 18 patients in the Study group and 21 in the control group; and grade 3 dermatitis was 3 patients in study group and 6 patients in the control group. None of the patients developed grade 4 dermatitis. The incidence of nausea and vomiting in study group was, grade 1 (22 patients), grade 2 (5 patients). Whereas 23 patients had grade 1 and fourteen patients had grade 2 nausea and vomiting in control group. No any patients had grade 3 & 4 nausea and vomiting in both groups. The result was statistically significant (p = 0.039). Grade 3 & 2 dysphagia was seen in 2 patients & 3 patients respectively in Study group, whereas in Control group 6 patients had grade 3 dysphagia and 7 patients had grade 2 dysphagia, however it was statistically not significant. There was no nephrotoxicity found in 47 (85.5%) patients in the Study group and 44 (80%) patients in the Control group, while 8 (14.5%) patients and 11 (20%) patients were found to have grade 1 toxicity in the Study and Control group respectively (p= 0.449). Thirteen patients in the Study group developed grade 2 anaemia and 2 patients in the Study group had grade 3 anaemia. 18 patients in the Control group developed grade 2 anaemia and 4 patients developed grade 3 anaemia. Blood transfusion was administered for anaemia. 5 patient developed grade 1 leukopenia in the Study group and 8 patients developed grade 1 leukopenia in control group. No systemic side effects were observed in both the arms.

The radiation reactions observed in the study group and control group were comparable apart from acute mucositis and vomiting where grade 3 reactions and grade 2 reactions, respectively showed statistically significant differences.

Table 1 Demographic Data

		Study Group (Arm A)	Control group (Arm B)
Mean Age		53.96 years	53.5 years
Gender	Male	52	49
	Female	3	6
Primary Site of Tumor	Oral Cavity	9	11
	Oropharynx	30	26
	Hypopharynx	11	6
	Larynx	5	12
AJCC Clinical Stage	Stage III	12	17
	Stage IV (A & B)	43	38

Table 2 Clinical Response to Treatment

	STUDY GROUP No. (%)				CONTROL GROUP No. (%)			
	CR	PR	SD	PD	CR	PR	SD	PD
At the completion of RT	34 (61.8%)	17 (31%)	2 (3.6%)	2 (3.6%)	32 (58.2%)	16 (29.1%)	4 (7.3%)	3 (5.4%)
At 3 months after completion of RT	36 (65.5%)	15 (27.3%)	2 (3.6%)	2 (3.6%)	35 (63.6%)	13 (3.6%)	4 (7.3%)	3 (5.4%)
At 6 months after completion of RT	36 (65.5%)	15 (27.3%)	2 (3.6%)	2 (3.6%)	35 (63.6%)	13 (23.6%)	4 (7.3%)	3 (5.4%)

Chi-square = 1.0236 P- value = 0.795
*CR- Complete Response, PR- Partial Response, SD- Stable Disease, PD- Progressive Disease

Table 3 Various Observed Toxicities (According to RTOG acute toxicity criteria)

	Study Group					Control Group					P-value
1. Grade 2. Toxicities	0	1	2	3	4	0	1	2	3	4	
3. Acute Dermatitis	3	31	18	3	0	1	27	21	6	0	0.474
4. Acute Mucositis	0	0	31	22	2	0	0	16	36	3	0.015
5. Nausea and Vomiting	28	22	5	0	0	18	23	14	0	0	0.039
6. Dysphagia	28	22	3	2	0	17	25	7	6	0	0.09
7. Nephrotoxicity	47	8	0	0	0	44	11	0	0	0	0.449
8. Anaemia	5	35	13	2	0	4	29	18	4	0	0.542
9. Leukopenia	50	5	0	0	0	45	8	2	0	0	0.337

DISCUSSION

Many chemotherapeutic agents like cisplatin, 5-FU, carboplatin, methotrexate, bleomycin, mitomycin have been used for CCRT schedules for the management of LAHNSCC patients, either as monotherapy or combination therapy to improve response of radiotherapy. However, cisplatin-based regimen for such patients offers an advantage of 8% overall survival which is the best among the above-mentioned agents according to *Pignon JP et al.* [4] In CCRT for head and neck cancer patients the standard regimen for chemotherapy is 100 mg/m2 cisplatin in both adjuvant [22] and definitive treatment [3,23], but severe grade III and IV toxicities in this schedule is the main limitation in treatment completion for majority of such patients. According to *Brizel DM et al.*,[24] only 60% of patients were able to complete the three weekly cisplatin schedule.

Nowadays, using various schedules of concurrent cisplatin with RT has become an area of interest to overcome the problem of increased acute toxicity. So, our study was intended to compare concomitant chemo-radiation using weekly Cisplatin versus three weekly Cisplatin in locally advanced head and neck cancer. In this study we had shown that weekly infusion of Cisplatin during standard radiotherapy is a promising and well tolerated regimen.

Sahoo TK et al [25] studied weekly vs three weekly cisplatin in head and neck cancer. Major toxicities included mucositis, dermatitis, vomiting, neutropenia, and anaemia. Grade 3 mucositis and Grade 3 vomiting were more in three weekly arm, although other grade 2 or 3 adverse events were also reported more in three weekly arm but not statistically significant. With a median follow-up of seven months complete response (CR) was 73.33% and partial response (PR)

was 26.67% in weekly arm; whereas in three weekly arm CR and PR were 85.71% and 14.29% respectively, which was not statistically significant. The complete response rate achieved in our study was 65.5%, which was also comparable to the results of*Ho KF et al.*,[19]*Sahoo T K et al*.,[25] and *Kose F et al* [26]. *Rawat S et al.,*[27]also compared toxicity, compliance, and early response in weekly (35mg/m^2) and 3-weekly (100mg/m^2) cisplatin administration concurrent with radiotherapy as definitive treatment of LASCHNC. They found that response was similar in both the arms (CR 66.7% vs 62.1%, p=0.2) after 3 months of treatment and no significant difference in grade 3 mucositis (75.9% vs 70%, p=0.2), but grade 3 neutropenia was more frequent in three weekly regimen (55.2% vs 26.7%, p=0.01). Completion rate of scheduled chemotherapy cycles was higher for patients receiving weekly regimen. Our study results were also suggested that there is a reduced need of hospitalization and supportive measures for patients receiving weekly cisplatin with RT (p=0.05).

Ho KF et al.,[19] found that it is possible to administration of higher mean cumulative doses of cisplatin with less toxicities in 40 mg/m^2,weekly schedule in comparison of 100 mg/m^2 three-weekly schedule. More delays (29% vs. 41%) and omission of chemotherapy (5.6% vs. 17.4%) occurred in the 3-weekly compared with the weekly regimen. In our study we found that among the in-field toxicities, mucositis is the commonest toxicity in both the arms, but the incidence of grade-III acute mucositis was found to be slightly higher in 3-weekly arm compared to weekly arm (65.5% v/s 40%) and grade IV mucositis was found in 5.5 % patients of 3-weekly arm compared to 3.6% patients of weekly arm. According to *Kose F et al.,*[26] and *Geeta SN et al.,*[28] mucositis was higher in weekly CCRT arm. *Rawat S et al.,*[27] showed similar results with our study. However, *Geeta SN et al.,*[28] found increased grade III skin and haematological toxicity in weekly cisplatin arm, whereas pharyngeal toxicities were higher in three weekly arm. They also noticed that weekly chemotherapy schedule was associated with higher rate of severe mucositis (p=0.005), more treatment interruptions and higher percentage of weight loss. Hence, they concluded that three weekly CT is less toxic than weekly and that weekly CT can be made more acceptable by reducing the dose and using feeding tubes for nutrition.

According to *Rawat S et al.,* [27]*Mitra D et al.,* [29] and *Azony AE et al*., [30] incidence of neutropenia was higher in 3-weekly chemotherapy arm. However, our study showed higher incidence of anaemia, thrombocytopenia and neutropenia in three-weekly CCRT arm compared to weekly CCRT arm but the difference was not statistically significant. Acute gastrointestinal toxicities (i.e. nausea, vomiting and diarrhoea) were significantly higher in three weekly arm, which was showed similarity with *Rawat S et al.,* [27] and *Azony et al.*[30] studies. About renal toxicity, our study showed that 3-weekly arm had higher incidence as compared to weekly arm (20% vs 14.5%) which was also similar with results of *Mitra D et al.,* [29] study.

In a meta-analysis by *Szturz P et al.,* [31]included 52 studies to compare the efficacy, safety, and compliance between these two approaches weekly verses three-weekly cisplatin for concurrent chemoradiation in LA-SCCHN. They found no difference in treatment efficacy as measured by overall survival or response rate between the chemoradiation settings with low-dose weekly and high-dose three-weekly cisplatin regimens. In the definitive treatment setting, the weekly regimen was more compliant and significantly less toxic with respect to high grade neutropenia ($p = .0024$), severe nausea and/or vomiting ($p < .0001$), and severe nephrotoxicity ($p = .0099$). Similar results were also observed in our study.

A prominent finding from our study was that weekly cisplatin arm patients had reduced requirement of feeding tube placement 58% in study group and 73% in 3-weekly group.

The clinical response rates obtained after 6 months of treatment follow up revealed that complete response (CR) rate was 36 patients (65.5%) in the Study group and 35 patients (63.6%) in the Control group. The partial response (PR) rates were 15 patients (27.3%) in Study group and 13 patients (23.6%) in Control group. Overall response OR rates (CR + PR) were 92.8% in the Study group and 87.2% in the Control group. Both CR and OR rates were found to be statistically not significant (p = 0.79).

Although some patients in our study arm sustained high local toxicity, mostly mucositis and vomiting, this was acceptable and comparable to the use of three weekly Cisplatin. No dose limiting systemic toxicity was encountered in our study.
As the sample size was comparatively small in our study, and the follow up period was of only six months, larger prospective randomized studies with longer duration of follow up with direct comparison of both of the regimens are needed for strong evaluation of efficacy & toxicity, and to draw inference about the late toxicities and also local regional control, disease free survival and overall survival.

CONCLUSION

Weekly cisplatin is a well-tolerated schedule with concurrent radiotherapy with almost similar efficacy as that of three-weekly schedule. Toxicity in terms of acute mucositis and vomiting was seen more in control group than study group, it was statistically significant, ($p < 0.015$) and ($p< 0.039$) respectively. Other acute toxicities like dermatitis, dysphagia and haematological toxicities like anaemia and leukopenia were seen in both groups, less in study group but statistically not significant and were manageable with simple supportive measures.
So, weekly cisplatin can be safely used with concurrent radiation in LAHNSCC, without potentiating toxicity and without compromising efficacy. However, large sample size and longer duration of follow up may be needed for strong evaluation of efficacy, toxicity profile, and to draw inference on LRC, DFS & OS.

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