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Weekly Versus three Weekly Concurrent Chemoradiotherapy in Upstaged Head and Neck Cancers-A Comparative Study

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Abstract

The head and neck cancers rank among the top 10 cancers globally. A huge population with newly diagnosed cancers is registered in India every year. Of these oral cancers are the most common in India. Surgery forms the mainstay of treatment. Concurrent chemoradiotherapy has shown better results in comparison to surgery alone in advanced cases. Cisplatin is the best radio sensitizer and has been accepted as the standard reference regimen. The present study was carried out to compare two different dosing schedules of cisplatin in terms of tolerance and response to the treatment. The present prospective, comparative study was carried out in the Department of Radiation Oncology, Government Cancer Hospital, Indore. 60 patients with local advanced head and neck cancers were included, divided into two arms. Arm-A with 30 patients received radical radiotherapy with cisplatin given every week during the radiotherapy sessions, while Arm-B patients received radical radiotherapy with concurrent cisplatin on day 1, 22 and 43. The RECIST 1.1 criteria was used for finding out the response. Proportional comparison was done using Pearson Chi-square test. There was a male preponderance in both the arms. 41.7% had moderately and 31.7% had poorly differentiated histological carcinoma grades. 55% had proliferative growth. 66.7% were in stage III and 33.3% were in stage IV disease. 60% in Arm-A and 70% in Arm-B had complete response. 10% in Arm-A and 3% in Arm-B had progression of the disease. Mucositis, dermatitis, xerostomia, trismus, dysphagia, anemia, thrombocytopenia, etc. all were comparable between the two arms ($p>0.05$). Our study found that cisplatin if given on day 1, 22 and 43 concurrently with radiation therapy has better outcome with lower incidence of disease progression.

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Key Words
Concurrent chemoradiotherapy, cisplatin, oral cancer, head and neck cancers

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INTRODUCTION

The head and neck cancers rank among the top 10 most common cancers globally and is more common in developing countries of Southeast Asia. In India, it accounts for nearly one-fourth of male and one-tenth of female cancers. There are 2.25 million people living in India with cancer according to Each year nearly 11.57 lakh new cancer cases are registered with around 7.84 lakh reported deaths annually[1].

Use of tobacco, areca nut, alcohol consumption, etc. Are the main causes of head and neck cancers. Oral cancer is the most common of the head and neck squamous cell carcinoma (HNSCC). The prevalence of this cancer in India differs from that of the western world. The Human Papillomavirus (HPV) has also been found to be a cause for head and neck squamous cell carcinoma (HNSCC)[2].

A multi disciplinary team approach is required for the management of head and neck cancers. Surgery, radiation therapy, chemotherapy and targeted therapy are the available treatment options. Surgery or radiation therapy by themselves or combination of these treatments may be a part of the treatment plan. Treatment is mainly dependent on the type and stage of head and neck cancers and other influencing factors are patient preference and the overall health.

The mainstay treatment for these cancers is surgery. In case of primary tumor, its complete removal along with local and regional extensions. Radiation therapy is given for organ and function preservation or as a substitute for surgery in unresectable tumors. In the early stages I and II of head and neck squamous cell carcinoma, chemotherapy has no role. Chemotherapy has shown benefit in cases with locally advanced disease, when it is used sequentially or concurrently with radiotherapy, with / without surgery[3].

Combination of cisplatin and radiotherapy is an effective and safe treatment in these patients in comparison to the radiation therapy alone[4]. In advanced III-IV B stages, concurrent chemo and radiation therapy (CCRT) has become a standard treatment option[5]. Many randomized studies have shown benefit of using chemotherapy along with radiation therapy over radiation therapy alone[4-7]. The use of concurrent chemoradiation has shown to be beneficial for organ preservation along with improvement in functional outcome and quality of life of survivors with good survival outcome when compared to surgery alone[8,9].

Cisplatin is the best radio sensitizer having all the mechanisms of interaction with radiation therapy. In cases with locally advanced head and neck squamous cell cancers concurrent use of cisplatin with radiation therapy (single daily fraction) has shown effectiveness (complete response rate) in the range of 65-75%[10].

Cisplatin in a dose of 100 mg/m^2 given every 3 weeks concurrently with radiation had been accepted as a standard reference regimen in head and neck squamous cell cancers, however, this dosage had led to high toxicity and issues with treatment compliance and hence the dose was modified and new strategy used weekly chemotherapy schedule with concomitant radiation therapy.

With the difference in the dosing schedule of cisplatin, in the present study we gave three courses of three weekly cisplatin (100 mg/m^2) versus 5-6 weekly cycles of 30 mg/m^2 of cisplatin along with concurrent radiation of 66-70 Gy to evaluate the dual role of cisplatin as a radiation sensitizer and potentiator and active drug itself. The objectives of the study included evaluation of tolerance of patients, response to the treatment and complications encountered.

MATERIAL AND METHODS

The present prospective, two-arm comparative study was conducted in the Department of Radiation Oncology, Government Cancer Hospital, M.G.M. Medical College, Indore (M.P.). A total of 60 patients with local advanced head and neck cancers were included. Prior to the conduct of the study Ethics Committee approval was obtained from the institution. The inclusion criteria was patient of either gender, of age >18 years and <70 years, Karnofsky performance status of 50 or more, histologically proven locally advanced head and neck cancer of stage III or IV and patient and/or his/her legally acceptable representative willing to provide voluntary written informed consent to participate in the study. The exclusion criteria being patient and/or his/her legally acceptable representative not willing for participation in the study, patient with age <18 and >70 years, patient with distant metastasis, having comorbidities such as uncontrolled hypertension, ischemic heart disease, diabetes mellitus and pulmonary tuberculosis, and patient who had undergone surgery or radiation therapy for head and neck cancer.

These 60 patients were randomized into two arms of 30 each using computer generated numbers. Arm-A (N=30): received radical radiotherapy of 66-70 Gy, 2 Gy/fraction, 5 fractions per week and concurrent chemotherapy with Inj. Cisplatin 30 mg/m^2 given every week during the radiotherapy session. Arm-B (N=30): received radical radiotherapy of 66-70 Gy, 2 Gy/fraction, 5 fractions per week with concurrent chemotherapy with Inj. Cisplatin 100 mg/m^2 on day 1, day 22 and day 43.

All the patients provided their voluntary written

informed consent prior to participation in the study. A detailed personal information including name, age, sex, address, contact number and all relevant details were recorded.

Each patient of either group received external beam radiotherapy with Theratron 780-C, Cobalt-60 Machine with 80 cm SSD and different portal according to the site and extent of primary disease. A total of 33-35 fraction doses of 6600-7000 cGy were given in 6-7 weeks with reducing field.

Inj. Cisplatin was given with 500 ml of normal saline over 2-3 hours as intravenous infusion with proper hydration, diuretics and antiemetics.

During the treatment, each patient was examined on a weekly basis for mucosal reaction, skin reaction, hematological toxicity, dysphagia, nausea and vomiting and renal toxicity. Complete hemogram and renal function test were done prior to each course of chemotherapy. Patients were instructed on nutrition and dental care. In case of confluent mucositis, treatment interruption was allowed to allow normal tissue reaction to heal.

All the patients were followed up at 0, 1 month and at 6 months.

Acute toxicities like mucositis, submucosal fibrosis, anemia, thrombocytopenia, dysphagia, leukopenia, dermatitis, renal toxicity and late toxicities like xerostomia, truisms and neuropathy were assessed according to the RTOG criteria.

Statistical Analysis: Proportional comparison between the two groups was done using Pearson chi-square test or Fisher's Exact test. Descriptive statistics were presented in the form of tables and graphs. A p value of <0.05 was taken as statistically significant.

RESULTS AND DISCUSSIONS

We had included 60 patients with locally advanced cases of head and neck cancers in the study, who were randomized to Arm-A (N=30) and Arm-B (N=30).

Majority of the patients were in the age group 40-49 (40%), followed by 50 years and above (33.3%).

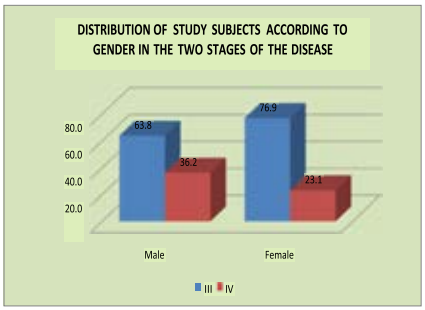

Fig. 1: Distribution of study subjects according to gender in relation to staging

There are less percentage of patients in the younger age group.

In Arm-A there were 80% males and in Arm-B, there were 76.7% males, the difference was found to be statistically not significant (p=0.754).

Overall, 26.7% patients had well-differentiated squamous cell carcinoma, 41.7% had moderately differentiated histological grade and 31.7% patients
had poorly differentiated histological grade. Overall, 45% patients had infiltrative type of
growth and 55% patients had proliferative type of growth.

The distribution according to primary site showed that 26.7% patients had primary site at buccal mucosa, 16.7% at tongue, 10% each at lower alveolus, base of tongue and larynx, respectively, 8.3% at soft palate, 5.0% each at floor of mouth, retro molar trigone and tonsil respectively. Only 3.3% patients had primary at upper alveolus. (Table 1)

Overall, 66.7% patients were in stage III and 33.3% patients in stage IV of the disease. There was no statistically significant difference in staging in relation to the gender (p=0.592). (Fig. 1)

All the males (100%) were bidi smokers and 61.8% males were tobacco chewers. In our study, 38.2% females were tobacco chewers.

71.7% patients were from rural areas and 28.3% patients were from urban areas. In both the areas, males were predominant and there was no statistically significant difference in the locality in relation to gender (p=0.557).

In Arm-A 16.7% patients and 6.7% patients in Arm-B had taken treatment gap, however, this difference was statistically not significant (p=0.42).

Overall, majority of patients in the age group 40-49 years had stage IV disease and in age group 50 years and above, majority of them had stage III disease. There was statistically significant association seen between the age groups and the staging of the disease (p=0.214).

The mean rank Karnofsky Performance Score in Stage III patients was 31.83, while in Stage IV patients it was 29.17. The difference was found to be statistically not significant (p=0.542).

In Arm-A, 60% patients had complete response, 23% had partial response, 7% patients had stable disease and in 10% patients the disease was progressive. In Arm-B, 70% patients had complete response, 20% had partial response, 7% patients had stable disease and in 3% patients the disease was progressive. Though in Arm-B, there was higher percentage of patients with complete response, the difference was not found to be statistically significant

The RECIST 1.1 criteria for categorizing response of target lesion was used for response evaluation.

Response Category	Recist 1.1
Complete response	Disappearance of all target lesions, plus reduction in short-axis diameter of pathologic lymph nodes to <10 mm
Partial response	> 30% decrease in the sum of the longest diameters of target lesions.
Stable disease	Neither partial response nor progressive disease
Progressive disease	> 20% increase (> 5% absolute increase) in the sum of the longest diameters, in comparison with the smallest sum of the longest diameters recorded since treatment started

Table 1: Distribution according to primary site

Primary Site	Frequency	Percentage
Alveolus Lower	6	10.0
Alveolus Upper	12	3.3
Buccal Mocosa	16	26.7
Base of Mongue	6	10.0
Floor of Mouth	3	5.0
Larynx	6	10.0
Retro molar Trigone	3	5.0
Soft Palate	5	8.3
Tongue	10	16.7
Tonsil	3	5.0
Total	60	100

Table 2 : Distribution according to treatment gap

	Group A	Group B			p-value Fishers exact test
Treatment Gap	Frequency	percentage	Frequency	percentage	
Yes	5	16.7	2	6.7	
No	25	83.3	28	93.3	0.42
Total	30	100	30	100	

Fishers Exact Test Applied. p-value=0.42, Not Significant:

Table 3 : Distribution according to treatment response

Response	Group A	Group B	Fisher's exact test p-value
CR	18 (60%)	21 (70.0%)	0.47, NS
PR	7 (23%)	6 (20.0%)	
SD	2 (7%)	2 (7%)	
PD	3 (10%)	1 (3%)	
Total	30 (100%)	30 (100%)	

Fisher's Exact test applied. P = 0.47, Not significant

(p=0.470). (Table 2)

In Arm-A, Grade 1 mucositis was seen in 26.7% patients, grade 2 in 40% patients, grade 3 in 30% patients and grade 4 in 3.3% patients. In Arm-B, Grade 1 mucositis was seen in 26.7% patients, grade 2 in 46.7% patients, grade 3 in 13.3% patients and grade 4 in 13.3% patients. There was no statistically significant association seen between mucositis and the arms (p=0.305). In Arm-A, Grade 1 dermatitis was seen in 30% patients, grade 2 in 53.3% patients and grade 3 in 16.7% patients. In Arm-B, Grade 1 dermatitis was seen in 33.3% patients, grade 2 in 60.0% patients and grade 3 in 6.7% patients. There was no statistically significant association seen between dermatitis and the arms (p=0.570).

In Arm-A, Grade 0 xerostomia was seen in 6.7% patients, grade 1 in 20.0% patients, grade 2 in 60.0% patients and grade 3 in 13.3% patients. In Arm-B, Grade 0 xerostomia was seen in 3.3% patients, grade 1 in 26.7% patients, grade 2 in 43.3% patients and grade 3 in 26.7% patients.

In Arm-A, Grade 0 trismus was seen in 3.3% patients, grade 1 in 3.3% patients, grade 2 in 30% patients and grade 3 in 53.3% patients. In Arm-B, Grade 0 trismus was seen in 3.3% patients, grade 1 in 3.3% patients, grade 2 in 40.0% patients and grade 3 in 36.7% patients. There was no statistically significant association seen between trismus and the arms (p=0.836).

In Arm-A, Grade 1 dysphagia was seen in 6.7% patients, grade 2 in 46.7% patients and grade 3 in 46.7% patients. In Arm-B, Grade 1 dysphagia was seen in 3.3% patients, grade 2 in 40% patients and grade 3 in 56.7% patients. There was no statistically significant association seen between dysphagia and the arms (p=0.694).

In Arm-A, Grade 1 anemia was seen in 50% patients, grade 2 in 30% patients, grade 3 in 16.7% patients and grade 4 in 3.3% patients. In Arm-B, Grade 1 anemia was seen in 43.3% patients, grade 2 in 20% patients, grade 3 in 30.3% patients and grade 4 in 6.7% patients. There was no statistically significant association seen between anemia and the arms (p=0.544).

In Arm-A, Grade 0 thrombocytopenia was seen in 66.7% patients, grade 1 in 23.3% patients and grade 2 in 10.0% patients. In Arm-B, Grade 0 thrombocytopenia was seen in 43.3% patients, grade 1 in 36.7% patients and grade 2 in 20.0% patients. There was no statistically significant association seen between thrombocytopenia and the arms (p=0.213).

In Arm-A, Grade 0 leukopenia was seen in 63.3%

patients, grade 1 in 13.3% patients, grade 2 in 13.3% patients, grade 3 in 6.7% patients and grade 4 in 3.3% patients. In Arm-B, Grade 0 leukopenia was seen in 36.7% patients, grade 1 in 20.0% patients, grade 2 in 20.0% patients, grade 3 in 13.3% patients and grade 4 in 10% patients. There was no statistically significant association seen between leukopenia and the arms (p=0.360).

In Arm-A, Grade 1 vomiting was seen in 23.3% patients, grade 2 in 33.3% patients and grade 3 in 43.3% patients. In Arm-B, Grade 1 vomiting was seen in 10% patients, grade 2 in 30% patients and grade 3 in 60% patients. There was no statistically significant association seen between vomiting and the arms (p=0.292).

In Arm-A, Grade 0 renal toxicity was seen in 70% patients, grade 1 in 20% patients, grade 2 in 6.7% patients and grade 3 in 3.3% patients. In Arm-B, Grade 0 renal toxicity was seen in 60% patients, grade 1 in 13.3% patients, grade 2 in 20.0% patients and grade 3 in 6.7% patients. There was no statistically significant association seen between renal toxicity and the arms (p=0.461).

In Arm-A, Grade 0 neuropathy was seen in 96.7% patients and grade 1 in 3.3% patients. In Arm-B, Grade 0 neuropathy was seen in 86.7% patients and grade 1 in 13.3% patients. There was no statistically significant association seen between neuropathy and the arms (p=0.353).

We had included patients with locally advanced head and neck cancers and were randomized to receive two different protocols of cisplatin concurrently with radiation therapy. As cisplatin has been reported to be the most effective agent in these patients having dual mechanism of actions- acts both as a radiation potentiator and sensitizer.

The most common age group seen in our study was 40-49 years followed by patients of age more than 50 years. There is a male predominance in comparison to the females. A vast majority of the males were tobacco chewers and bidi smoking are seen in all the males. According to a study, tobacco was the causative agent for cancers in 48.2% males and 20.1% females[11].

Majority of the patients had moderately differentiated squamous cell carcinoma, followed by poorly differentiated and well-differentiated. Higher prevalence of proliferative type of growth is seen. Higher percentage of population was from rural area in comparison to the urban area.

Buccal mucosa was the commonest site of primary, followed by tongue, lower alveolus, base of tongue, larynx, soft palate, floor of mouth, retromolar trigone, tonsil and upper alveolus.

Majority of these patients were in Stage III, followed by Stage IV. Stage IV was more commonly seen in patients of the age 40-49 years and Stage III in patients of age 50 years or more.

Higher percentage of patients from Arm-A had taken treatment gap in comparison to Arm-B patients, though this difference is not statistically significant (p=0.42). Our results are supported by Tsan *et al*.[12]

The mean rank Karnofsky Performance score was higher in patients who were in Stage III in comparison to the Stage IV patients, though the difference being not statistically significant (p=0.542).

Majority of the patients in both the arms had complete response to the given treatment, with a slightly higher proportion in Arm-B in comparison to Arm-A. A very low proportion of patients of Arm-B had progressive disease. However, no association could be established between response and the arms (p=0.470). Mitra *et al*[13] reported complete response in 76% patients of three weekly arm and 67% patients of weekly arm, which is quite comparable with our study findings.

Grade 2 mucositis was more prevalent in both the arms, followed by Grade 3 in Arm-A and Grade 1 in Arm-B. Gupta *et al*[14] reported higher prevalence of grade 3 in weekly arm, which is contradictory to our findings and Tsan *et al*[12] reported grade 3 toxicity in three-weekly arm, which is also contradictory to our study results.

Dermatitis was more commonly seen in grade 2 in both the arms. While the studies done by Gupta *et al*[14] and Tsan *et al*[12] reported higher prevalence in Grade 3 toxicity, which differs from our study findings.

Grade 2 xerostomia was more commonly seen. Prakash *et al*[11] in their study found significant difference in xerostomia between weekly and three-weekly arms which is contradictory to our study findings, where we found no significant difference (p>0.05). Noronha *et al*[15] found higher prevalence of grade 2 toxicity, which is comparable to study findings. Grade 3 trismus was more common in Arm-A and Grade 2 was more common in Arm-B. Our results corroborate with the study done by Noronha *et al*.[15] Grade 3 dysphagia was more common in both the arms, which is supported by results of study done by Prakash *et al*.[11]

Grade 1 anemia was commonly seen in both the arms. Noronha *et al*[15] reported higher prevalence of grade 2 in once-weekly arm and grade 2 and 3 in three-weekly arm, which contradicts our findings.

Grade 0 thrombocytopenia and leukopenia respectively were more common in both the arms. Mackiewicz *et al*[16] reported differing findings in their study. Noronha *et al*[15] reported prevalence of leukopenia to be grade 2 in weekly once arm and grade 2 and 3 in three-weekly arm, which contradicts our findings.

Grade 3 vomiting was more common in both the arms, which is supported by study of Noronha *et al*[15] who also found higher prevalence of Grade 2 and 3 vomiting in their study.

Grade 0 renal toxicity was more common in both the groups. Mitra *et al*[13] supported our results.

Grade 0 neuropathy was seen in majority of the patients of both the arms, the results corroborate with the study done by Noronha *et al*.[15]

In our study we found that toxicities showed no statistically significant association with the arms ($p>0.05$).

The limitations the study was that the sample size was too small to extrapolate the results and the follow-up was short.

CONCLUSION

From the results obtained we can conclude that three-weekly arm gave better results in comparison to the weekly treatment arm. Cisplatin added concurrently to radiation therapy has proven its affect in both the types of treatment arms with a good compliance of the patients. The three-weekly treatment with cisplatin can be confidently given even in a low resource setting. Although the treatment outcome was better in three-weekly arm, there was higher incidence of toxicities like higher grade mucositis, dermatitis, vomiting and hematological toxicities were seen in comparison to weekly arm.

We highly recommend the use of concurrent chemotherapy with radiation therapy using a three-weekly protocol for the treatment of patients with locally advanced head and neck cancers.

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