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ORIGINAL ARTICLE

PROSPECTIVE STUDY COMPARING SINGLE-AGENT VERSUS DOUBLET-AGENT CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED ORAL CAVITY AND OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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ABSTRACT:

Introduction: Concurrent chemoradiotherapy is the standard treatment for locoregionally advanced oropharyngeal and unresectable oral-cavity cancers. This study aims to make a comparative analysis of the efficacy and toxicity of single-agent chemoradiotherapy with weekly cisplatin versus doublet-agent chemoradiotherapy with cisplatin and 5-FU in locoregionally advanced oral-cavity and oropharyngeal cancer. **Patients and Methods:** In this open label randomised study, 60 patients with histologically proven Stage III – IVA oral-cavity and oropharyngeal cancer were randomly assigned between May 2013 and July 2014 to receive chemoradiation to a dose of 66-70 Gy in 33-35 fractions over 7 weeks with either weekly cisplatin 40 mg/m^2 (Arm A) or weekly cisplatin 40 mg/m^2 and 5-fluorouracil 375 mg/m^2(Arm B). The tumorresponse, treatment compliance and toxicity profile were investigated. **Results:** Longer overall treatment time resulting from more treatment interruptions were associated with eight patients in Arm A(27.5%) and 15 patients in Arm B (51.7%) ($p<0.060$). The compliance to chemotherapy was superior in patients receiving weekly cisplatin alone with 22 patients receiving more than five cycles of chemotherapy as compared to 16 patients in Arm B (75.8% vs 55.1%). Sixteen patients in Arm A (55.1%) and 21 patients in Arm B (72.4%) developed grade 3-4 mucosal toxicity. Sixteen patients in Arm A (53.3%) and 11 patients in Arm B (36.6%) achieved complete response to treatment, whereas, ninepatients in Arm A (30%) and nine patients in Arm B (30%) had a partial response to treatment. ($p=0.195$) **Conclusion:** Doublet-agent chemoradiotherapy led to frequent treatment interruptions because of higher rates of acute mucosal, skin and haematological toxicity, thus leading to prolongation of overall treatment time, over the standard single-agent weekly cisplatin and did not confer any benefit in loco-regional tumour control.

Key words: Chemoradiotherapy; Tumorresponse; Oropharangeal

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INTRODUCTION

Head and neck squamous cell carcinoma is one of the commonest cancers in India and of all the new cases diagnosed globally, approximately 25 % are from India.[1]Cancer of the oral cavity makes up approximately 30% of head and neck region tumours in United States,[2] whereas oropharyngeal cancers account for approximately 10% of the annual worldwide incidence of head and neck squamous cell carcinomas,[3] and grouped together, are the sixth most common cancer worldwide. Only 10-15% of the patients present with early stage (stage I/II) disease and nearby 60 % of the patients present with locoregionally advanced disease (stage III/IVA/IVB). Locoregional failure constitutes the predominant recurrence pattern and most fatalities result from uncontrolled local and/or regional disease.[4]

The past 15 years have seen extensive exploration of concurrent chemoradiotherapy as definitive management for patients with locoregionally advanced squamous cell head and neck cancer. The goal of definitive concurrent chemoradiotherapy can be briefly summarised as to increase survival by improving locoregional control and decreasing possibility of micrometastasis to distant organs while preserving normal tissue integrity and function. Three clinical rationales support the use of chemotherapy delivered concurrently with radiation. First, concomitant chemoradiotherapy can be used with organ-preserving intent, resulting in improved cosmesis and function compared with surgical resection with or

without adjuvant treatment. Second, chemotherapy can act as a radiosensitizer, improving the probability of local control and, in some cases, survival, by aiding the destruction of radioresistantclonogens. Third, chemotherapy given as part of concurrent chemoradiation may act systemically and potentially eradicate distant micro-metastases.[5] In a nut-shell, concurrent chemoradiotherapy attempts to capitalize on the tumour-radiosensitizing properties of chemotherapy, in addition to potentially delivering active agents that function systemically.

Multiple highly effective chemoradiotherapy treatment platforms exist, but, unfortunately, the optimum timing, dosing and choice of systemic agents, are controversial. Radiation therapy and concurrent high-dose single-agent cisplatin have been established as the standard of care in selected patients with locoregionally advanced head and neck cancer.[6] Although squamous cell carcinomas of the oral cavity and oropharynx are sensitive to several anticancer drugs, the unresolved issue remains whether to use single agent or a combination of two or more drugs.

This prospective, comparative analysis of outcomes between two chemoradiotherapy regimens, single agent (cisplatin alone) versus doublet chemotherapy (cisplatin and 5-fluorouracil), aims to answer the former question and in the process further explore the realm of treatment intensification to improve therapeutic gain in locoregionally advanced oral cavity and oropharyngeal cancers.

PATIENTS AND METHODS

Study Design

Patients

Between May 2013 and July 2014, sixty patients with histologically proven stage III – IVA (locoregionally advanced) oral cavity and oropharyngeal squamous cellcarcinoma were randomized to two different regimens of definitive chemoradiotherapy comprising of 30 patients in each group. (i.e. radiotherapy with weekly cisplatin vs radiotherapy with weekly cisplatin plus 5-fluorouracil).

Patients had ECOG performance score 0-1 and adequate haematologic (haemoglobin >10 gm/dl, absolute neutrophil count >1500/l, platelets >100,000/ll), hepatic and renal function (calculated creatinine clearance >60 mL/min). Exclusion criteria included stage IVB disease, carcinoma of lip, presence of distant metastasis, previous treatment with RT or chemotherapy, any prior or synchronous malignancy, hypersensitivity to platinum agents and serious medical disease or pregnant state. The study was carried out only after the protocol was approved by the institution's ethics review committee.

Radiation

All patients were simulated on Simulator CT after immobilisation with a thermoplastic mould and treated withCo-60 gamma-rays. The enlarged lymph nodes were delineated by lead markers externally before simulation. Patients were treated by parallel opposed lateral portals in both arms without any tissue compensators. Nodes were treated electively in all patients. In both the treatment arms, 36-40 Gy / 20 fractions / 4 weeks was given to the primary and draining lymph nodes (phase I) followed by 20 Gy / 10 fractions / 2 weeks after sparing the spinal cord (phase II) and final 6 - 10 Gy / 3-5 fractions (phase III) was delivered through additionally reduced portals with a margin of 2 cm around the original gross tumour.

Chemotherapy

Patients were divided in the following treatment arms –

Arm A – Concomitant weekly cisplatin (40 mg/m^2)

Arm B – Concomitant weekly cisplatin (40 mg/m^2) + 5-fluorouracil (375 mg/m^2)

A complete haemogram and renal function tests were done before every cycle of chemotherapy. Chemotherapy was withheld in cases of any grade 2 or more haematologic or renal toxicity, till the normal values were recovered after specific management. Prophylactic anti-mycotics and salt gargles were started for patients in both the treatment arms.

Response Assessment

Tumor response was evaluated after completion of treatment by clinical examination and imaging studies (CT/MRI head and neck region). The best tumour response at 6 weeks from completion of treatment was recorded and used for the assessment using RECIST criteria (Response evaluation criteria in solid tumors) version 1.1.

Acute and late treatment toxicities and follow *up*

Patients were monitored for mucosal and skin reactions atleast weekly during radiotherapy. Prophylactic anti-mycotics were initiated in all the patients. The severity of acute toxicities was scored using the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.03.

The first clinical follow up was scheduled at six weeks and thereafter every two months for a period of one year. All the patients were clinically examined in joint tumour board and response was assessed clinically and radiologically. Local control for the purpose of this study was determined by clinical and radiological freedom from tumour above clavicles. Persistence of disease was considered as local and regional failure. Fine needle aspiration cytology or a biopsy was carried out to document a recurrence in clinically suspicious cases.

Late toxicities were scored at each follow-up evaluation according to CTCAE scale. Detailed statistical analysis was performed for patients with more than 6 months of complete toxicity data to study differences in toxicity profile between the two treatment arms.

Statistical Analysis

Statistical analysis was conducted using the statistical package for the social science system (SPSS) version 17. Frequency tables with counts and percentages were used to describe pre-treatment and treatment characteristics

for patients in both treatment groups. The nominal categorical characteristics between the two treatments were compared using chi-square test or fisher's exact test as appropriate. For continuous variables, mean and median values were compared between the groups using the *t*-test. A *p*-value of < 0.05 was considered statistically significant.

RESULTS

Patient cohort and characteristics

Patients were well balanced between the two groups in terms of age, sex, subsite involvement and stage distribution (Table 1).

Treatment Compliance

In our study, we observed that median overall treatment time in patients receiving cisplatin (Arm A) was 51 days and in those receiving both 5-FU and cisplatin (Arm B) was 53 days. The mean ± SD for Arm A was 51.20 ± 2.37 days and the range was 47-57 days. While for Arm B the mean was 53.44 ± 3.83 days and the range was 47-60 days. The difference between the two treatment arms was found to be statistically significant (p = 0.010). Majority of patients in the study completed the planned treatment. Patients who were able to complete their treatment within the stipulated time plus a 5 day allowance for logistical problems and public holidays were considered to have completed on time. Eight patients in Arm A (27.5%) had prolongation of treatment time, whereas, 15 patients in Arm B (51.7%) completed treatment with an unacceptable delay of more than 5 days because of more frequent treatment interruptions. The median length of prolongation was seven days for patients in Arm A, while for patients in Arm B it was ten days. The difference between the two arms was not found to be statistically significant (p = 0.060).

The compliance to chemotherapy was assessed, using the number of patients who were able to receive five cycles of weekly chemotherapy, as a surrogate. Twenty-two patients in Arm A (75.8%) received five or more cycles of chemotherapy, whereas, 16 patients were able to receive five or more cycles in Arm B (55.1%). The most common reason for poor compliance to chemotherapy was inadequate hematologic parameters and severe asthenia.

Twelve patients in Arm A (41.3%) whereas twenty patients in Arm B (68.9%) required hospital admission for supportive care during the treatment course. The most common reasons for hospital admission were grade 2 or more hematologic toxicity, grade 3-4 mucosal toxicity, and dysphagia requiring nasogastric tube placement and parenteral nutrition. (Table 2A)

Acute Toxicity Profile

High rates of grade 3-4 acute mucosal reactions were seen in patients receiving chemoradiation with cisplatin and 5-FU (Arm B). Of the analyzable 29 patients who received weekly cisplatin, 16 patients (55.1%) had grade 3-4 mucositis, whereas 21 of those receiving doublet agent chemotherapy (72.4%) developed grade 3-4 mucositis. The acute toxicity rates were an indicator of poor compliance towards doublet agent chemotherapy given concomitantly with radiotherapy in our patient population. The percentage of patients with grade 3-4 skin reactions, dysphagia, diarrhoea and also grade 2 or more hematotoxicity was higher in cisplatin plus 5-FU group. (Table 2B)

Treatment related mortality i.e death during or within 1 month after treatment was seen in one patient of doublet-agent chemoradiation (3.4%) arm in contrast to none in single-agent chemoradiation arm.

Response to treatment

The response to treatment, in our study, was assessed at 6 weeks after therapy according to RECIST criteria version 1.1. Both clinical and radiological findings were employed for response assessment.

The tumour response at the end of six weeks from therapy completion served as the primary end point. Overall, the complete remission rate for locoregional disease was comparable (p = 0.195) between the treatment groups. Sixteen patients in Arm A (53.3%) and eleven patients in Arm B (36.6%) achieved complete response to treatment. Nine patients in Arm A (30%) and nine patients in Arm B (30%) had a partial response to treatment. One patient in Arm A (3.3%) and one patient in Arm B (3.3%) presented with progressive disease. In 3 patients in Arm A and 7 patients in Arm B, response could not be classified as either partial response or progressive disease. (Table 3)

Attempt for salvage therapy

In patients with residual tumour, disease recurrence, or progression of disease, salvage surgery or palliative treatment was offered depending on the performance status of the individual patient, symptoms and previous treatment, after multidisciplinary tumour board meeting. Three patients, of the eighteen patients who had a partial response, exhibited clinical evidence of persistent nodal disease with complete remission of local disease 6 weeks after radiotherapy and underwent neck dissection.

DISCUSSION

Concurrent chemoradiotherapy has a central role in the management of locoregionally advanced head and neck cancer and a survival benefit for this approach in comparison to radiation alone is now widely accepted.[7] Concurrent chemoradiotherapy attempts to capitalize on the tumor-radiosensitizing properties of chemotherapy, in addition to potentially delivering active agents that function systemically. Overwhelmingly, trial results have indicated that the concurrent addition of chemotherapy sensitizes tumours to radiation and increases locoregional control and thereby survival. Although the collective data are strong in establishing the superiority of the combination of radiation with concurrent chemotherapy relative to standard radiation fractionation alone in the management of locally advanced HNC, there is variability in clinical trials in patient selection and

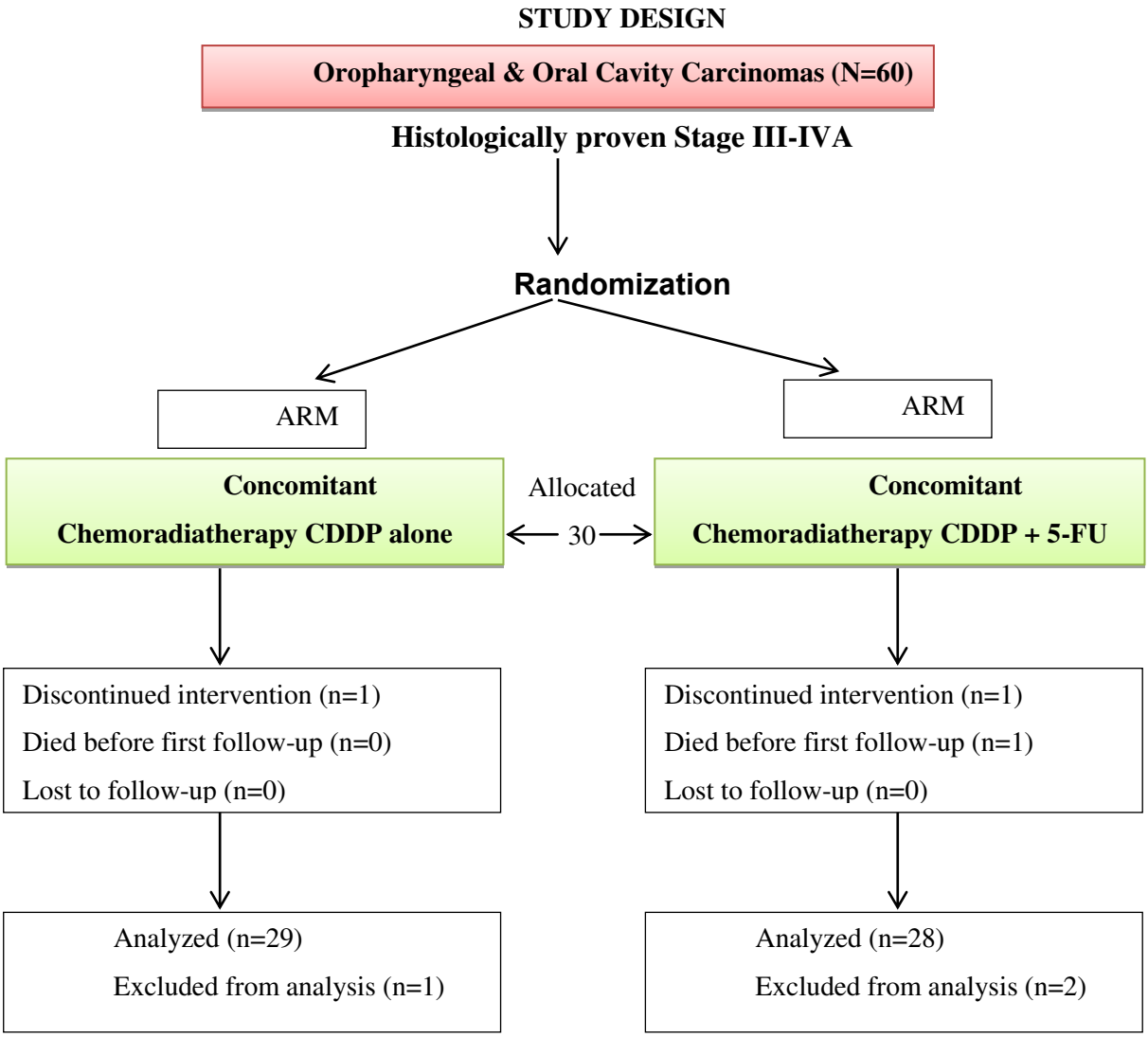

Figure 1: Flowchart showing study design

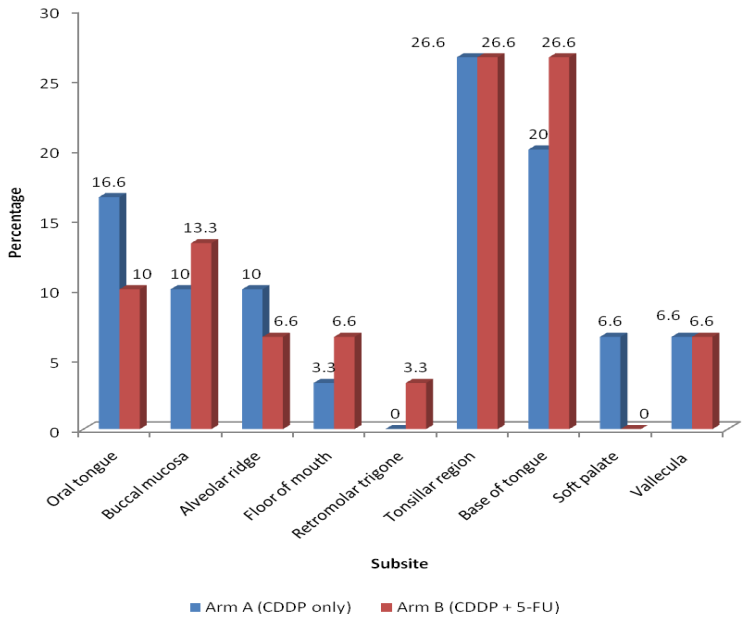

Figure 2: Distribution of patients according to subsite involved

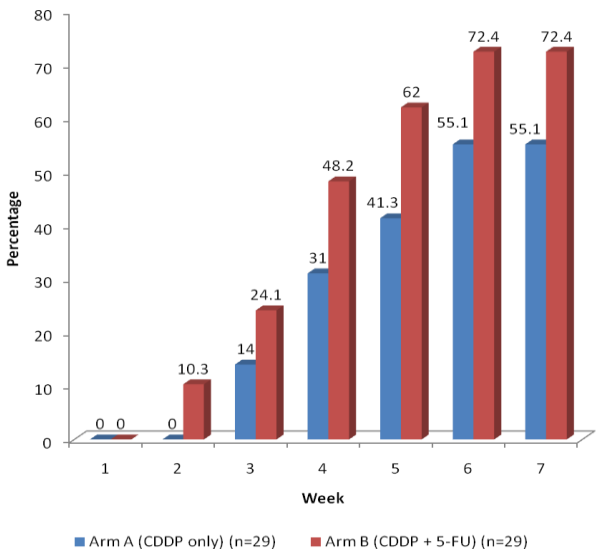

Figure 3: Weekly analysis of Mucositis Grade 3-4

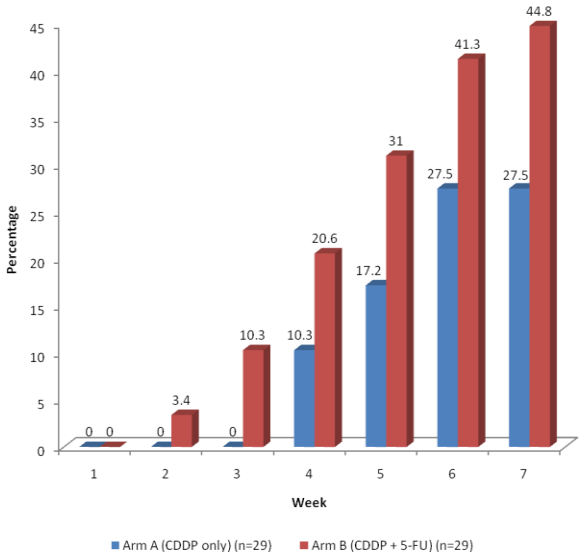

Figure 4: Weekly analysis of Hematotoxicity Grade 2-3

Table 1: Baseline characteristics of the patients

	Arm A (CDDP only)		Arm B (CDDP + 5-FU)		Total	
	n	%	n	%	n	%
Sex						
Male	26	86.6	27	90	53	88.3
Female	4	13.3	3	10	7	11.6
Age (in years)						
31-40	3	10	4	13.3	7	11.6
41-50	6	20	7	23.3	13	21.6
51-60	12	40	8	26.6	20	33.3
61-70	9	30	11	36.6	20	33.3
Tumour size (T stage)						
T1	1	3.3	0	0	1	1.6
T2	5	16.6	6	20	11	18.3
T3	13	43.3	14	46.6	27	45
T4a	11	36.6	10	33.3	21	35
T4b	0	0	0	0	0	0
Nodal stage (N stage)						
N0	3	10	2	6.6	5	8.3
N1	13	43.3	15	50	28	46.6
N2	14	46.6	13	43.3	27	45
N3	0	0	0	0	0	0
Stage						
III	16	53.3	13	43.3	29	48.3
IV A	14	46.6	17	56.6	31	51.6

n – number of patients
CDDP – Cisplatin
5-FU – 5-fluorouracil

Table 2: Comparison of overall treatment time

OTT (Days)	Arm A (CDDP only)	Arm B (CDDP + 5-FU)	*p*-value
Mean ± SD	51.20 ± 2.37	53.44 ± 3.83	**0.010**
Median	51	53	
Range	47 – 57	47 - 60	

Table 3: Comparison of parameters of treatment compliance

	Arm A¥ (CDDP only) (n=29)		Arm B‡ (CDDP + 5-FU) (n=29)		Total (n=58)		p-value
	N	%	N	%	N	%	
Treatment prolongation							
Delay > 5 days	8	27.5	15	51.7	23	39.6	
Median prolongation	7 days		10 days				0.060
No. of chemotherapy cycles received							
≥ 5	22	75.8	16	55.1	38	65.5	0.090
< 5	7	24.1	13	44.8	20	34.4	
Hospital admission	12	41.4	20	69	33	56.8	0.035

Table 4: Comparison of acute toxicity profile

	Arm A (CDDP only) (n=29)		Arm B (CDDP + 5-FU) (n=29)		Total (n=58)		P value
	N	%	N	%	N	%	
Mucositis Grade							
0	0	0	0	0	0	0	-
1	0	0	0	0	0	0	
2	13	45	8	28	21	36.2	
3	14	48	18	62	32	55.1	
4	2	7	3	10	5	8.6	
Dermatitis Grade							
0	0	0	0	0	0	0	-
1	7	24.1	2	6.8	9	15.5	
2	13	44.8	11	37.9	24	41.3	
3	8	27.5	13	44.8	21	36.2	
4	1	3.4	3	10.3	4	6.8	
Hematotoxicity Grade							
0	12	41.3	4	13.7	16	27.5	-
1	9	31.0	12	41.3	21	36.2	
2	6	20.6	9	31.0	15	25.8	
3	2	6.8	4	13.7	6	10.3	
4	0	0	0	0	0	0	
Dysphagia Grade							
0	0	0	0	0	0	0	0.079
1	4	14	1	3	5	8.6	
2	15	52	10	34	25	43.1	
3	10	34	18	62	28	48.2	
4	0	0	0	0	0	0	
Diarrhoea Grade							
0	25	86.2	10	34.4	35	60.3	<0.001

Table 5: Comparison of tumor response 6 weeks from treatment completion

Response group	Arm A¥ (CDDP only) (n=29)		Arm B‡ (CDDP + 5-FU) (n=28)		Total		*p*-value
	N	%	N	%	N	%	
Complete response	16	53.3	11	36.6	27	47.3	
Partial response	9	30	9	30	18	31.5	
Stable disease	3	10	7	23.3	10	17.5	
Progressive disease	1	3.3	1	3.3	2	3.5	0.582
Unevaluable	1	3.3	2	6.6	3	5.2	

regimens, leading to continuing debate as to which combined regimen should be considered standard. Multiple highly effective chemoradiotherapy treatment platforms exist, but, unfortunately, the optimum timing and choice of systemic agents still remain controversial issues. To the best of our knowledge, no randomized trial has made an adequate and direct comparison between cisplatin alone versus cisplatin and 5-FU chemoradiotherapy. Centeredaround the ongoing debate of whether single-agent cisplatin-based chemoradiotherapy or doublet-agent chemoradiotherapy platforms are preferred, our study aimed to assess the feasibility of both the regimens and make a comparative analysis of tumour response and toxicity profile in locoregionally advanced oral cavity and oropharyngeal cancers.

Although multiple randomised trials[9,10]and meta-analyses[11,12]have favoured concurrent platinum chemoradiotherapy in treatment of locally advanced oral cavity and oropharyngeal cancers, but at the cost of increased toxicity which is exaggerated in frail patients, and therefore, whether treatment intensification by further accentuating the chemotherapy in a chemoradiotherapy regimen will have significant benefit in Indian population, is a relevant question and which has largely remained unanswered.Therefore, a pragmatic approach is to evaluate alternative and viable chemoradiotherapy schedules to aim for superior response rates and yet maintain favourable toxicity profile. This present study aims to comparatively analyse the tumour response and toxicity profile of two different chemoradiotherapy regimens in locoregionally advanced oral cavity and oropharyngeal cancers, using conventionally fractionated radiotherapy for both the groups.

Patients included in the study were treated with same radiotherapy dose and conventional fractionation schedule i.e. to a total dose of 70 Gy in 2 Gy per fraction 5 days a week. Conventional fractionation was chosen as the fractionation schedule as the implementation of altered fractionation as a routine practice is yet to be established. Strict selection of patients, inherent inconvenience due to daily multiple fractions and a greater rate of acute reactions, particularly acute radiation mucositis, were the main reasons for adopting conventional fraction to be coupled with chemotherapy in our study.[13]

In our study comparing the two chemoradiotherapy regimens, we observed significantly poor treatment compliance in the patients receiving doublet-agent chemotherapy with higher treatment interruptions and hospital admissions. This was reflected in the statistically significant prolongation of the overall treatment time in doublet agent chemoradiation group (53 days) over single-agent chemoradiation group (51 days) ($p<0.010$). The median prolongation of treatment time in patients receiving only cisplatin was 7 days, whereas, it was 10 days for patients receiving both cisplatin and 5-FU.

The compliance to chemotherapy was assessed, using the number of patients who were able to receive five cycles of weekly chemotherapy, as a surrogate. Regarding cisplatin based chemoradiotherapy, data in literature has suggested that a cumulative dose of 200mg/m^2 is sufficient to yield beneficial antitumour effect.[14] Since in this study we used cisplatin at 40mg/m^2 weekly, patients who were able to receive five or more cycles of either weekly cisplatin (Arm A), or, weekly cisplatin and 5-fluorouracil (Arm B) were said to be compliant to chemotherapy. Of the 58 patients who completed planned treatment, 20 patients (34.4%) could not receive the cumulative dose threshold of 200mg/m^2, seven patients in Arm A and 13 patients in Arm B.The most common reason was inadequate hematologic parameters and severe asthenia.However, the compliance to chemotherapy in our study was fairly similar to some of the published data of chemotherapy compliance in literature.[15]

Not unexpectedly, high rates of grade 3-4 acute mucosal reactions were seen in patients receiving chemoradiation with cisplatin and 5-FU (Arm B). Of the analyzable 29 patients in Arm A, 16 patients (55.1%) had grade 3-4 mucositis, whereas in Arm B, 21 patients (72.4%) developed grade 3-4 mucositis.Evidence from multiple randomized trials have suggested that acute mucositis constitutes the most significant impediment to the timely delivery of concurrent chemoradiotherapy because of frequent treatment interruptions, and the resulting prolongation of treatment time adversely affects the success of radiotherapy in achieving local and regional control because of accelerated clonogen repopulation.[16,17]In our study, the most common cause for poor compliance to chemotherapy was inadequate hematologic parameters. Grade 2-3 hematologic toxicity was observed in eight patients of Arm A (27.5%), whereas, in 13 patients of Arm B (44.8%). This difference was not found to be statistically significant. Nine patients in Arm A (31.03%) and 12 patients in Arm B (41.3%) had Grade 1 hematotoxicity. We also observed that 12 patients in Arm A (41.3%) did not have any decrease in cell counts or anemia during the complete treatment course, while this number was only four for patients in Arm B (13.7%). This difference was found to be statistically significant between the two treatment groups. None of the patients in our study developed grade 4 hematotoxicity.

In our study, we observed that only four patients who had received cisplatin based chemoradiotherapy (Arm A) developed diarrhea. In Arm A, 25 patients were free from diarrhea throughout the treatment (86.2%), whereas, in Arm B, only ten patients (34.4%) could complete the treatment without any increase in stools passed per day over pre-treatment. This difference was found to be statistically significant ($p<0.0001$).

Late toxicity scoring in our study was based on a minimum of six months of toxicity evaluation. The follow-up of the present study was relatively short and prevents us from commenting on longer evaluation of toxicity profile. The comparative analysis of xerostomia rates in the two chemoradiation groups revealed that there was a lack of association between the

chemotherapy used and the severity of xerostomia. Although, theoretically, late effects might have a consequential evolution from the persistent severe acute effects, but interestingly, multiple studies have confirmed that, compared with radiation alone, the long-term side effects of concurrent chemoradiotherapy, such as on swallowing function or speech, are not increased.[18]Deasy JO et al suggested that patient factors (age and gender) and the use of chemotherapy are typically not correlated with xerostomia risk.[19]Unarguably, late toxicity is a significant issue when comparing any new radiotherapy or chemoradiotherapy regimen against the standard in head and neck cancers and it has been established by the GORTEC and RTOG studies that concurrent chemoradiotherapy is associated with higher late toxicity (Machtay M et al,2008 ; Denis F et al,2003).[20,21] In our study, higher rates of late toxicities in the form of grade 3 xerostomia, grade 2/3 dysphagia and grade 2 dysguesia were observed in the doublet-agent chemoradiation arm (46.4%, 35.7% and 78.5%, respectively) as compared to cisplatin-based chemoradiotherapy (31%, 17.2%, and 72.4%), although the difference was not statistically significant.

The response to treatment was assessed at six weeks after therapy according to RECIST criteria version 1.1. The follow-up of the study was relatively short and prevents us from commenting on the long term disease free and overall survival. Overall, the complete remission rate for locoregional disease was comparable (p = 0.195) between the treatment groups. Sixteen patients in Arm A (53.3%) and 11 patients in Arm B (36.6%) achieved complete response to treatment. Nine patients in Arm A (30%) and nine patients in Arm B (30%) had a partial response to treatment. Three patients, of the eighteen patients who had a partial response, exhibited clinical evidence of persistent nodal disease with complete remission of local disease 6 weeks after radiotherapy and underwent neck dissection.

In our study, complete responses were seen in 16 patients (53.3%) receiving weekly cisplatin alone concurrent with radiotherapy. This was found to be lower than the complete response rate observed by Sharma A et al, in their phase II trial, which compared the effectiveness and tolerance of weekly cisplatin-based chemoradiotherapy to radiotherapy alone in advanced carcinoma of oropharynx and nasopharynx. They observed a complete response rate of 80.5% in patients who received weekly cisplatin along with radiotherapy.[22]Asin this study, 3.9% patients had stage II disease and 37.7% patients had nasopharyngeal carcinoma, a definite and valid comparison of complete response rates was not possible.

Though, the complete response rates of our study, in patients receiving weekly cisplatin as radiosensitizer, were found to be higher than that reported by the Head and Neck Intergroup study by Adelstein et al. They identified a complete response rate of 40.2% for the group of patients treated with radiotherapy and concurrent weekly cisplatin.[6]

Treatment related mortality i.e death during or within 1 month after treatment was seen in one patient of doublet-agent chemoradiation (3.4%) arm in contrast to none in single-agent chemoradiation arm. High 30-day mortality with chemoradiation has also been reported in another phase II trial although different in clinical design, it highlighted the risks of giving intensive schedules without adequate supportive care infrastructure, especially in patients with a poor nutritional reserve.[23]

The follow-up of the present study was relatively short and prevents us from commenting on the long term disease free survival, overall survival, and a more comprehensive evaluation of the late toxicities too. Further validation along with longer follow up results will add to the robustness of our data and will be presented in due course of time.Another limitation of our study was the relatively smaller sample size and consequently, subgroup analyses could not be materialised. Finally, HPV status of majority of the oropharyngeal cancer patients was unknown. Though, most of our patients had tobacco related cancer, this still remains one of the major limitations of this study, as HPV has proven to have both prognostic as well as predictive roles in oropharyngeal cancers. Nevertheless, taking into account the social conditions, nutritional status of our patients and infrastructure in a developing country like ours, this study does bring to our notice the importance of the question asked and has shown that solely accentuating the chemotherapy in a chemo-radiotherapy regimen may not bring forth the desired increase in the therapeutic index.

CONCLUSION

Doublet-agent chemoradiotherapy using weekly cisplatin and 5-FU, in our study, did not confer any benefit in locoregional tumour control over the standard single-agent weekly cisplatin chemoradiotherapy. Complete locoregional responses for the patients receiving cisplatin-only chemoradiation were higher than for patients receiving cisplatin and 5-FU chemoradiation (53.3% versus 36.6%) although the difference was not statistically significant.

Addition of weekly 5-FU led to frequent treatment interruptions due to the higher rates of acute mucosal, skin and haematological toxicities. Hospital admissions and supportive care required because of grade 3-4 mucosal toxicity and grade 2 or more hematological toxicity were significantly more for patients receiving both cisplatin and 5-FU. The resulting prolongation of overall treatment time in the doublet-agent chemoradiation group over the single-agent chemoradiation group, in our study, was statistically significant (p=0.01). Thus, the intensification of chemoradiation by the addition of 5-FU led to a significant increase in the overall treatment time, possibly offsetting any benefit from radiosensitization and increased systemic action, because of the accelerated repopulation of the surviving clonogens in the tumour.

Studies with larger sample sizes and longer follow-up should be instituted for further validation of the

feasibility of multi-agent chemoradiotherapy in locoregionally advanced oral cavity and oropharyngeal carcinomas.

REFERENCES

1. Wei Wi. Commentary: head and neck carcinomas in the developing world. Br Med J 2002; 325: 827.
2. Greenlee RT et al. Cancer statistics, 2000. CA Cancer J Clin 2000; 50(1): 7-33.
3. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61(2): 69–90.
4. Vokes EE et al. Head and neck cancer. N Engl J Med 1993; 328: 184–194.
5. Seiwert TY et al. The concurrent chemoradiation paradigm—general principles. Nat ClinPractOncol 2006; 4: 86–100.
6. Adelstein DJ, Li Y, Adams GL, 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 ClinOncol 2003; 21: 92-98.
7. Bourhis J et al. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy [abstract]. J ClinOncol 2004; 22: 5505.
8. Adelstein DJ. Systemic chemotherapy for squamous cell head and neck. Expert OpinPharmacother 2003; 4: 2151-2163.
9. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999; 91(24): 2081–2086.
10. Jeremic B et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J ClinOncol 2000; 18: 1458–1464.
11. 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. RadiotherOncol 2009; 92(1): 4–14.
12. Browman GP et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. Head Neck 2001; 23: 579–589.
13. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J RadiatOncolBiolPhys 2000;48(1):7–16.
14. Ang KK. Concurrent radiation chemotherapy for locally advanced head andneck carcinoma: are we addressing burning subjects? J ClinOncol 2004; 22: 4657–9.
15. Bahl M, Siu LL, Pond GR, et al. Tolerability of the Intergroup 0099 (INT 0099) regimen in locally advanced nasopharyngeal cancer with a focus on patients' nutritional status. Int J RadiatOncolBiol Phys 2004;60:1127–36.
16. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumorclonogen repopulation during radiotherapy. ActaOncol 1988; 27: 131-146.
17. Cox JD, Pajak TF, Marcial VA, et al. Interruptions adversely affect local control and survival with hyperfractionated radiation therapy of carcinomas of the upper respiratory and digestive tracts. New evidence for accelerated proliferation from Radiation Therapy Oncology Group Protocol 8313. Cancer 1992; 69: 2744–2748.
18. Seiwert TY, Salama JK, Vokes EE. The chemoradiation paradigm in head and neck cancer. Nat PractClinOncol 2006; 4: 156-171.
19. Deasy JO, et al. Radiotherapy dose-volume effects on salivary gland function. Int J RadiatOncolBiol Phys 2010; 76(3): S58–S63.
20. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J ClinOncol 2008; 26: 3582–9.
21. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J RadiatOncolBiol Phys 2003; 55: 93–8.
22. Sharma A, Mohanti BK, Thakar A, et al. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. Ann Oncol 2010; 21(11): 2272–2277.
23. Kumar S, Pandey M, Lal P, et al. Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial. Radiother Oncol 2005; 75: 186–92.

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