RADICAL RADIOTHERAPY WITH CONCURRENT WEEKLY CISPLATIN IN LOCO-REGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK- A SINGLE INSTITUTION EXPERIENCE

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ABSTRACT

BACKGROUND

Concurrent chemotherapy by three weekly high dose cisplatin along with radical external beam radiation therapy is the standard of care for the treatment of Locally Advanced Squamous Cell Carcinoma of Head and Neck Cancers (LASCCHN). But this treatment regime is having certain disadvantages such as high toxicity profile, increased treatment cost and increased overall duration of treatment. Hence, the present study was undertaken to determine the acute toxicity and tumour response in Locally Advanced Head and Neck cancer (LASCCHN) patients who were treated with concurrent chemoirradiation using 30 mg/m^2 weekly cisplatin.

MATERIALS AND METHODS

This single institution Prospective study included data of 60 patients who presented to Govt. Royapettah Hospital with locally advanced and unresectable (Either AJCC 8th Edition stage III or stage IV) stage and previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and maxillary antrum with age between 18 yrs. and 60 yrs of either gender. They were treated with intent of radical external radiation therapy with 66 Gy-70 Gy in 33-35# over 6-7 weeks and concurrent chemotherapy (Inj. Cisplatin 30 mg/m^2) which was given weekly once to a total of six cycles and they were assessed for immediate response and toxicity and were analysed after four to six weeks of completion of treatment.

RESULTS

The mean age of the patients was 49.6 years. The most common site of involvement was tongue. The mean overall treatment time was 56.9 days. Out of sixty available patients, 26 (43%) patients showed complete response. Partial response was seen in 22 (37%) patients with an overall response rate of 80%. Twelve patients (20%) showed loco regional failure. The median radiotherapy dose was 70 Gy and median number of chemotherapy cycles was 6 (range 1–7). According to the Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria, acute grade 3 or worse mucositis and dermatitis was seen in 10 (17%) and 9 (15%) patients respectively, essentially in patients receiving doses ≥66 Gy. Organ injury was assessed using the Common Terminology Criteria for Adverse Events (CTCAE). Other toxicities (hematologic, nausea and vomiting) were found to be mild and self limiting. Chemotherapy is used to achieve maximum local control. Thus, comparatively newer modalities of concurrent chemo-radiation particularly with Cisplatin and its combinations are giving increasingly rewarding results, by way of producing high loco regional control with significantly improved survival rates.

CONCLUSION

In this study, we found radical radiotherapy with concurrent low dose weekly cisplatin is having moderate efficacy. Toxicity levels were found to be within acceptable limits.

KEY WORDS

Squamous Cell Carcinoma, Head and Neck Cancers, External Radiation, Inj. Cisplatin.

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BACKGROUND

Globally lip, Oral cavity, and pharyngeal cancers have been estimated to be responsible for 529, 500 incident cases and 292, 300 deaths in 2012, accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths.[1]

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In Developing countries, risk factors for Oral cavity and oro pharyngeal cancers also include the chewing of betel nut with or without tobacco (Oropharyngeal and Oral cavity cancers). Traditionally Surgery or Radiation Therapy (RT) alone are curative for early stage disease in more than 95% of cases. They are used in combination for loco regionally advanced head and neck cancer with high rate of success.[2,3] In LASCCHN locoregional failure is more expected which lead to increased risk of distant metastases.[4] Recent developments show radical radiotherapy with 3-weekly high-dose cisplatin is now considered the standard of care in LASCCHN.[5-7] Even though the role of chemotherapy as sensitiser exists, there is difficulty in choosing the optimal CRT schedule because of the heterogeneity of study designs and different ways of combining chemotherapy with RT.[8]

Hence the present study aimed to assess the usefulness and feasibility of concurrent chemotherapy Inj. Cisplatin 30 mg/m^2 given weekly once to a total of six cycles along with external radiotherapy dose of 66-70 Gy in 33-35 fractions over six to 7weeks in advanced unresectable head and neck cancers and to assess the immediate loco-regional response and acute toxicity 4-6 weeks after completion of RT.

MATERIALS AND METHODS

Study Design

A Prospective longitudinal observational study was done among patient in Govt. Royapettah Hospital with locally advanced and unresectable (Either AJCC 8th Edition stage III or stage IV) previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and maxillary antrum of either gender after obtaining written informed consent. Patients considered eligible were those with age between 18 years to 60 years who was previously untreated with a proven histology of squamous cell carcinoma of the head and neck. They were treated with intent of radical external radiation therapy with 66 Gy-70 Gy in 33-35# over 6-7 weeks and concurrent chemotherapy (Inj. Cisplatin 30 mg/m^2) which was given weekly once to a total of six cycles and they were assessed for immediate local/locoregional response and toxicity profile. All data were tabulated in Microsoft Excel and analysed with SPSS (Statistical Package for Social Sciences) software version 20(IBM Corporation, USA). Data were analysed with suitable test and interpreted as frequencies and percentages.

Radiotherapy

All patients underwent radiation treatment conventionally with Telecobalt machine (Theratronix 780, Canada) because of its energy profile comparable to that of a 4MV linear accelerator. All patients were immobilised with thermoplastic mask. The gross tumour volume was contoured in Oncentra Treatment Planning System (Version 4.3, Elekta, Veenendaal, the Netherlands) as per the RTOG Contouring Guidelines and it was given a total dose of 66 or 70 Gy in 33- 35 fractions. The Initial phase 46 Gy was delivered in 23 fractions to the mid-plane with pair opposing lateral fields in select sites. The lower neck whenever indicated, was treated with a matched low anterior neck field up to a dose of 50 Gy in 25 fractions normalized at 2-3 cms.. of depth. In the second phase, off-cord technique was used to deliver the radiation dose to the primary tumour site along with the nodal sites with a 2-3 cms. margin upto a dose of 66 or 70 Gy.

Chemotherapy

Chemotherapy 30 mg/m2 weekly cisplatin was administered intravenously during the course of RT along with hydration which was given with one litre of normal saline and 500 ml of DNS along with premedication was through steroids and antiemetics. Chemotherapy administration was withheld if the Hb% level was less than 8 gm/dl or due to febrile neutropenia or serum creatinine was more than 1.5 mg%, till recovery.

Patient Evaluation

After completion of chemoradiation, all patients were followed up after one month for the next two months to assess the locoregional response and acute toxicity. All acute toxicities were recorded according to the Radiation Therapy Oncology Group (RTOG) guidelines. Disease control was assessed clinically or with CT/MRI with contrast and DL-scopy whenever indicated till two months from the completion of treatment. The response to treatment were graded as complete response (CR) or partial response (PR) and no response (NR).

Statistical Analysis

All data were tabulated in Microsoft Excel and analysed with SPSS (Statistical Package for Social Sciences) software version 20(IBM Corporation, USA). Descriptive statistics was done using frequency tables.

RESULTS

The study period was from May 17 to April 2018. Sixty-three individuals were included for the study among which three discontinued the chemo-radiation due to toxicity and hence, were excluded from the study. So, the data of remaining sixty patients were considered for analysis.

All patients were assessed for immediate loco regional response and acute toxicity to chemo-radiation. Age of the participants ranged between 28 years and 60 years out of which 83% (50) of them were female and 17% (10) were male. Habit of smoking and alcohol consumption was found among 33% (20) of followed by Tobacco or betel nut chewing by 20% (12), and individuals who do all the above three were 13% (8). 4 participants had none of the above-mentioned habits. Karnofsky Performance Status of 60% (36) individuals were 80 followed by 30% (18) Individuals had 70 and 10% (6) were more than 90.

	n (%)
1. Age	
Mean	49.6 years
Range	28- 60 years
2. Sex	
Male	50 pts (83 %)
Female	10 pts (17 %)
3. Prevalence of Habits in our Patients	
Habits	
Smoking only	10 (17%)
Alcohol only	0 (0%)
Tobacco/ Betel-nut chewing	12(20%)
Smoking + Alcohol	20 (33%)
Smoking + tobacco chewing	6 (10%)
Alcohol + tobacco chewing	0 (0%)
All the three	8 (13%)
Nil	4 (7%)
Total	**60 (100%)**
4. Karnofsky Performance Status:	
Score	
>90	6 (10%)
80	36 (60%)
70	18 (30%)

Table 1. Baseline Characteristics

Primary Site			
1. Anterior 2/3rd of tongue	12 (20%)		
2. Hypopharynx	10 (17%)		
3. Alveolus	8 (14%)		
4. Tonsil	6 (10%)		
5. Buccal mucosa	6 (10%)		
6. Floor of mouth	6 (10%)		
7. Posterior 1/3rd of tongue	6 (10%)		
8. Maxilla	2 (3%)		
9. Posterior pharyngeal wall	2 (3%)		
10. Retro molar Trigone	2 (3%)		
Histology			
Differentiation Grade			
Well differentiated	30 (50%)		
Moderately differentiated	10 (16%)		
Poorly differentiated	14 (24%)		
Undifferentiated	6 (10%)		
Staging			
TNM Staging			
N Stage		**T Stage**	
	T2 (%)	T3 (%)	T4 (%)
No			2 (3%)
N1		6 (10%)	10 (17%)
N2a	2 (3%)	4 (7%)	2 (3%)
N2b		2 (3%)	2 (3%)
N2c	6 (10%)	6 (10%)	12 (20%)
N3		2 (3%)	4 (7%)
Total	**8 (13%)**	**20 (33%)**	**32 (54%)**

Table 2. Distribution of Subjects according to Primary Site, Histology and TNM Staging. n = 60

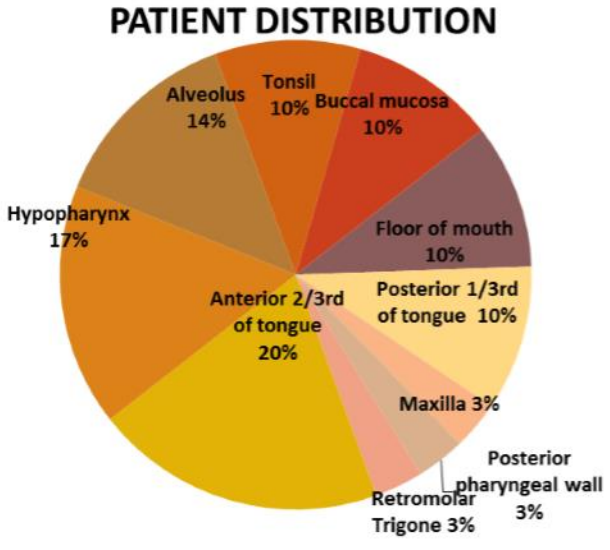

Figure. 1

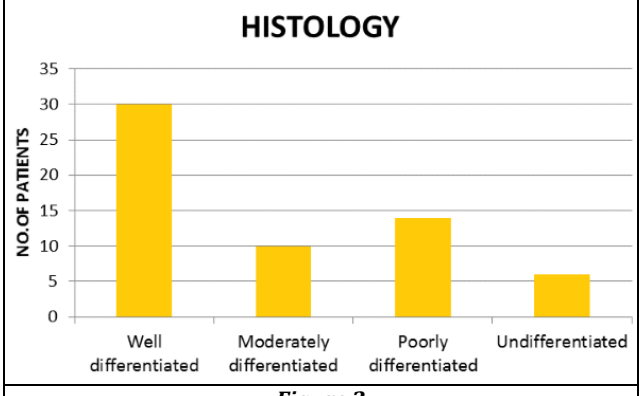

Figure 2

Primary Site	Total no of Pts.	Complete Response	Partial Response	Static Disease
Ant. 2/3rd tongue	12	4 (33%)	4 (33%)	4 (33%)
Hypopharynx	10	4 (40%)	4 (40%)	2 (20%)
Alveolus	16	4 (25%)	4 (25%)	8 (50%)
Tonsil	6	4 (67%)	2 (33%)	
Buccal mucosa	6	2 (33%)	4 (67%)	
Floor of mouth	6	4 (67%)	2 (33%)	
Post 3rd tongue	6	2 (33%)	2 (33%)	4 (33%)
Maxilla	2		2 (100%)	
Post pharyngeal wall	2	2 (100%)		
Retromolar trigone	2	2 (100%)		

Table 3. Response Rate by Patient Characteristics

In present study, there were 60 evaluable patients of which 50 were males and 10 were females. Eight patients presented with T2 N2 lesion, twenty patients with T3 any N and Thirty-two patients with T4 any N lesions. Out of eight patients in T2 group, 6 (75%) pts. showed complete response and 2 (20%) showed partial response and 2 (10%) showed static response. In T4 group out of 32 patients, we observed complete response in only 6 (19%) patients. Partial response was seen in 16 (50%) patients. Static response was observed in 10 (31%) patients. In all the three groups, disease progression was not observed in any patient.

According to stage grouping, eight patients were in stage T2 N2. Six patients (75%) patients showed complete response. Two (25%) patient showed partial response.

The addition of concomitant boost radiation before there In T3 N1 disease there were 6 patients. CR was observed in 4 (67%) pts and PR in 2 (33%) patient. In T3 N2 group there

were 12 pts. CR was seen in 8(67%) pts and PR in two (16%) patient. Two patients (17%) had static disease. In T3 N3 Lesion the only two are available patient showed complete response. The N3 node completely regressed.

In T4 N0 Lesions, only two patients were available. He showed complete response. In

T4 N1 group, 10 patients were available, of them 2(20%) patient showed CR and 6(60%) patients showed PR. two patients (20%) had static disease. In T4 N2 disease, we treated 16 patients. Two (13%) patients showed CR. Eight (50%) patients showed PR and 6 (37%) patients showed only less tumour and nodal shrinkage without any progression of disease. Out of four patients with T4 N3 very advanced cancer, two showed partial response and the other two had static disease (Table. 2).

	Patient Characteristics	Total Evaluable Pts.	Complete Response No. of pts. (%)	Partial Response no. of Pts. (%)	Overall Response no. of Pts. (%)	Static Response No. of Pts. (%)
Gender	Male	50	24 (48%)	18 (36%)	42 (84%)	8 (16%)
	Female	10	2 (20%)	4 (40%)	6 (60%)	4 (40%)
	Total	60	26(43%)	22(37%)	48 (80%)	12 (20%)
T Stage	T2N2	8	6 (75%)	2 (25%)	8 (100%)	
	T3	20	14 (70%)	4 (20%)	18 (90%)	2 (20%)
	T4	32	6 (19%)	16 (50%)	22 (69%)	10 (62%)
	Total	60	26 (43%)	22 (37%)	48(80%)	12 (40%)
Stage Grouping	T2 N2	8	6(75%)	2 (25%)	8 (100%)	
	T3 N1	6	4 (67%)	2(33%)	6 (100%)	
	T3 N2	12	8 (67%)	2(16%)	10 (83%)	2 (17%)
	T3 N3	2	2		2 (100%)	
	T4 N0	2	2		2 (100%)	
	T4 N1	10	2 (20%)	6 (60%)	8 (80%)	2 (20%)
	T4 N2	16	2 (13%)	8 (50%)	10 (63%)	6 (37%)
	T4 N3	4		2 (50%)	2 (50%)	2 (50%)
	Total	**60 (100%)**	**26 (43%)**	**22 (37%)**	**48 (80%)**	**12 (20%)**

Table 4. Distribution of Subjects based on Gender, T Staging and Stage Grouping with Response Rate

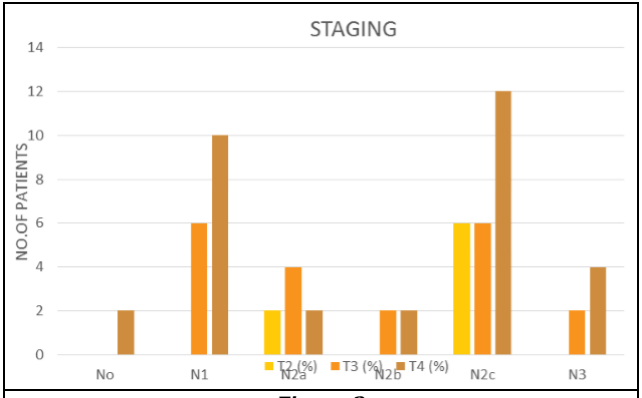

Figure 3

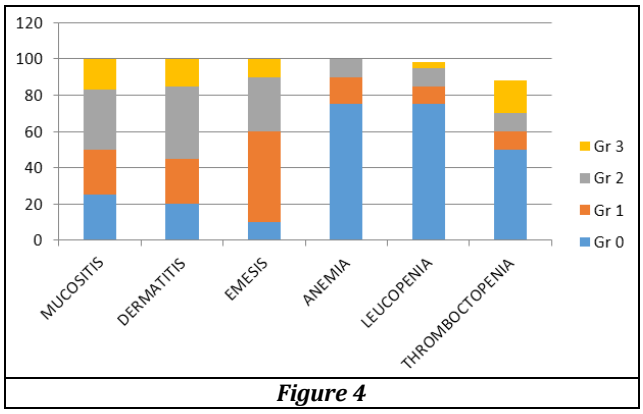

Figure 4

Toxicity Analysis

Table 5 shows the acute toxicity among the Study subjects. Acute grade 3 mucositis was seen in 10 (17%) and Grade 2 dermatitis 24 (40%) patients respectively, essentially in patients receiving doses ≥66 Gy to 70 Gy and 6 or more cycles of chemotherapy. Other toxicities were mild and self-limiting and managed conservatively. The incidence of CTC grade 3 leucopenia was seen in 3(5%) patients. No episodes of febrile neutropenia or grade 3 thrombocytopenia reported in our analysis. Interruption or compromise in the planned dose of radiotherapy because of toxicity was seen in 12 (20%) patients. Supportive care was given to six (10%) patients. This regime was well tolerated with limited acute toxicity.

Side Effects	Grade 0	Grade 1	Grade 2	Grade 3
Mucositis	15 (25%)	15 (25%)	20 (33%)	10 (17%)
Dermatitis	12 (20%)	15 (25%)	24 (40%)	9 (15%)
Emesis	6 (10%)	30 (50%)	18 (30%)	6 (10%)
Anemia	45 (75%)	9 (15%)	6 (10%)	NIL
Leucopenia	45 (75%)	6 (10%)	6 (10%)	3(5%)
Thrombocytopenia	30 (50%)	6 (10%)	6 (10%)	18 (30%)

Table 5. Acute Toxicity among the Study Subjects

DISCUSSION

The more popular regime of cisplatin with a dose of 30-40 mg/m2 is given weekly outside the context of clinical trials.[9] Because of single inter group trial there was a bias towards using weekly cisplatin.[10] The outcome is same for 60 evaluabe patients in the study of concurrent weekly cisplatin with conventional fractionated radiation therapy . The Sharma el al.[11] phase III study of 153 patients with stage II-IV oropharyngeal and nasopharyngeal cancer showed good response rates of 72 &9.2% against 69& 7% for concurrent weekly cisplatin as compared to radical radiation therapy only. They were more frequent discontinuation of treatment due to higher grade III-IV toxicities in the two arms. The recent generation co-operative group trials are also tried with weekly carboplatin along with taxanes or only carboplatin in combined chemo radiation treatment of locoregionaly advanced squamous cell carcinoma of head and neck cancer as definite treatment or after induction chemotherapy.[12] The altered fractionation shows improvement in the treatment for SCCHN as per the recent evidences.[13] There exists significant improvement in the

treatment outcomes with concurrent chemotherapy with altered fractionation shedules.[14,15] With the cost of increased acute and late toxicity by the addition of concomitant boost radiation there is evidence of significant acceptance by the study group as per Kumar et al analysis.[16,17] Due to the lower toxicity of weekly cisplatin in the dose given when compared to high dose cisplatin the acceptance is more with the clinicians in terms of toxicity profile.

CONCLUSION

The efficacy of this regimen is largely comparable to other contemporary regimes. Weekly cisplatin along with radiation marginally improved survival rate and quality of survival but has minimal toxicity profile when compared to three weekly regimes. Larger prospective trials are needed in order to find the most optimal way of combining the drug with radiation therapy in the management of Locally Advanced Squamous Cell Carcinoma of Head and Neck (LASCCHN)

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