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Comparative study of quality of life, toxicity in weekly cisplatin vs three weekly cisplatin along with radiation in locally advanced head and neck malignancies

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ABSTRACT

Aim: This was a prospective two arm comparative study of quality of life, toxicity and response in patients of locally advanced head and neck cancers treated with concurrent chemoradiation with either three weekly or weekly Cisplatin. **Materials and methods:** The study was performed during 18 months period, 50 patients of locally advanced head and neck cancer were divided into two arms of 25 patients each. All the patients received conventional radiotherapy on linear accelerator with 6MV photons for a total dose of 66Gy, 2Gy per fraction for 33 fractions. Patients in Arm A received concurrent chemotherapy with three weekly Cisplatin at a dose of 100mg/m2 on day 1, 22 and 43. Patients in Arm B received concurrent chemotherapy with Cisplatin at a dose of 40mg/m2 given weekly. **Results**: All the patients completed the planned radiotherapy treatment except one patient in Arm A who died during RT. The mean cumulative dose was slightly higher in the weekly arm. RT delay and omission of chemotherapy was more common in the three weekly arm. Compliance to treatment was marginally better in the weekly arm. Response to chemoradiation was slightly better in arm B which was not statistically significant. Acute toxicities were slightly higher in the three weekly arm compared to the weekly arm but statistically insignificant. QOL scores were poorer for patients in the three weekly arm. Patients in the weekly arm reached baseline QOL scores compared to the three weekly arm. **Conclusion**: Patients who are nutritionally compromised and economically backward, radical radiation with weekly concurrent Cisplatin is a viable and an effective treatment option.

Key words: Chemoradiation, Cisplatin, Global health scores.

Introduction

Head and neck cancers squamous cell carcinomas are the sixth most common cancer in the world and a major health problem worldwide. In India alone, it is the most common cancer with three-fourths of the patients presenting in an advanced stage. Among the HNSCCs, cancer of oral cavity and oropharynx predominates our population. The prognosis of these patients depends on various factors like age of the patient, site of the tumour, size of the tumour, thickness of the tumour, degree of differentiation and spread into regional lymph nodes[1]. Poverty, illiteracy, advanced stage at presentation, lack of access to health care, and poor treatment infrastructure pose a major challenge in management of these cancers. As per the estimate provided by the International Agency for Research on Cancer based GLOBOCAN 2012, head and neck cancers account for almost 173,224 new cases annually in females and 513,104 new cases in males. The mortality rates are high, with almost 284555 males and 91110 females dying from the disease annually worldwide. In India the agency reports an incidence of 111,073 in males and 33654 in females annually, accounting for 22.2% and 7.32% of cancer related mortality in males and females respectively. The burden of HNSCCs is on the rise with control of infectious diseases and increased longevity of the growing population. With their distinct demographic profile, risk factors, food habits, family and personal history,

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HNSCCs are emerging as major health problems which are lifestyle related, have a lengthy latent period and need dedicated infrastructure and human resource for treatment [2].The treatment of patients with locally advanced HNSCCs has evolved since the introduction of combined modality treatment for these patients. During the last quarter of a century, clinical trials for patients with HNSCCs have demonstrated progress in treatment outcomes, including better control, lower incidence of systemic recurrences, improved disease free survival and most importantly improved overall survival. The quality of life has improved for many of these patients, especially when the larynx and voice function is preserved in cases of larynx and hypopharynx. The concept of concurrent chemotherapy with radiation was revisited in 1980s with the introduction of Cisplatin given concurrently with radiation therapy as the primary treatment for patients with inoperable or unresectable head and neck cancers. The rationale of such treatment is to increase local control by overcoming radio resistance and to eradicate systemic micro metastasis. Cisplatin is probably the best currently available radiosensitizer and it possess all the mechanisms of interaction with radiation therapy. The clinical CR rate obtained with concurrent Cisplatin and radiation therapy (single daily fraction) in patients with locally advanced HNSCCs is in the range of 65% to 75%. Cisplatin has been administered in various schedules weekly, daily, days 1 to 5 every 4 weeks, and every 3 weeks. The addition of another agent or agents in combination of cisplatin (e.g.: 5 FU, taxanes) concomitant with radiation therapy did not add to the clinical CR rate but increased local side effects, especially mucositis [3].Thus Cisplatin alone appears to be the chemotherapeutic agent of choice for concurrent chemotherapy with radiation therapy in HNSCCs. At present Cisplatin alone given at dose of 100mg/m^2 on a 3 week schedule is the standard in developed nations. Although efficacious, this is associated with considerable acute morbidity necessitating intensive supportive care which is problematic especially in countries with limited resources. Thus arises the need to explore alternative chemotherapy schedules including concurrent weekly Cisplatin based radical radiotherapy schedules which give comparable if not superior results in countries where most patients are nutritionally compromised and economically backward.

Materials and methods

This was a prospective two arm comparative study done in the Department of Radiotherapy, Mehdi Nawaz Jung Institute Of Oncology and Regional Cancer Center. Following ethics committee approval 50 patients of locally advanced head and neck squamous cell cancers who underwent treatment from the Department of Radiation Oncology from March 2014 to August 2015 were enrolled in the study.

Inclusion Criteria: Age less than 70 years, patients presenting with a locally advanced stage and histopathologically proven head and neck squamous cell carcinoma, ECOG performance status of 0-2, complete blood picture with haemoglobin > 10g%, total white blood cell count of >4000cells/mm^3, platelet counts of >1.5 lakh/mm^3, renal parameters with blood urea < 40 mg/dl and serum creatinine <1.5 mg/dL, patients with informed consent.

Exclusion Criteria: Age greater than 75 years, performance status ECOG PS >2, tumors with histology other than squamous cell carcinoma**,** patients who had prior underwent surgery or neoadjuvant chemotherapy for the tumour. patients unlikely for active follow-up**.** A standardized data collection proforma was used for the study which incorporated thorough history and physical examination including appropriate endoscopic assessment if indicated. All the cases underwent biopsy or FNAC for confirmation of malignancy. All basic investigations were done including Chest X Ray PA view. Computer tomography scan of head and neck site was done for location and extent of the disease**.** Dental evaluation as a part of pre-RT dental prophylaxis after assessing the clinical stage and deciding the definitive treatment**.** The patients who fulfilled the inclusion criteria as well their attendants/care takers were elaborately explained about the stage and nature of the disease, the treatment details regarding concurrent chemo radiation, its effectiveness and the possible side effects in their own vernacular language.

A total of 50 patients of locally advanced head and neck squamous cell carcinoma were randomised into:

ARM A: consisting of 25 patients receiving Radical Radiotherapy of 66Gy, 2Gy/ fraction, 5 fraction per week and concurrent chemotherapy with Inj.Cisplatin 100mg/m2 given on day 1,22 and 43.

ARM B: consisting of 25 patients receiving Radical Radiotherapy of 66Gy, 2 Gy/ fraction, 5 fractions per week and concurrent chemotherapy with Inj. Cisplatin 40mg/m2 given every week during radiotherapy.

CISPLATIN was administered with normal saline and given over 2 to 3 hrs IV infusion. It was followed by radiotherapy within 1 hr after completion of infusion. Myelosuppression and renal toxicity were evaluated by doing complete haemogram, blood urea and serum creatinine weekly. All the patients underwent

compulsory weight recording every 7 days. Chemotherapy dose was appropriately corrected when there was a change in BSA due to changes in weight.

CISPLATIN Regimen:
Injection – Ranitidine 50 mg.
Injection – Dexamethasone 8 mg.In 100 ml normal saline over 15 minutes.
Injection – Ondansetron 8mg.

The two arms were compared using chi square test to check whether they were balanced in terms of patient and disease related characters like stage, sex, tumor site, performance status and age. Response to treatment was assessed based on WHO criteria and analysis was done using descriptive statistics and compared between the arms using Chi square test.Toxicity was assessed using common toxicity criteria (CTCAE.V3) and analysis was done using descriptive statistics by using the available charts. The maximum grade of toxicity was also studied compared between the two arms with chi square test. Quality of life assessment was done at completion of treatment, 4 weeks and 8 weeks follow up using EORTC QLQ-C30 and EORTC QLQ-H&N35 and was compared with the baseline QOL scores in all patients. The QOL scores were compared between two arms using nonparametric tests-Mann Whitney test.

Results

The two groups were analyzed for comparability using a cross table analysis (Chi square test) and the two groups were comparable in terms of age, sex, site of tumor, stage and performance status.

Table 1: Patient Characteristics

Characteristics	ARM A	ARM B
No Of Patients	25	25
Median Age (Years)	51	50
Age Range (Years)	29 - 61	28 - 65
Male: Female	21:04	20:05
ECOG PS1	22	22
ECOG PS2	3	3
STAGE		
III	14	15
IVA/IVB	11	10
Tumour site		
Oral Cavity	17	18
Tongue	5	5
Buccal Mucosa	9	9
Alveolus	3	4
Oropharynx	3	2
Tonsil	1	1
Base of tongue	2	1
Larynx	3	3
Supraglottis	2	3
Glottis	1	0
Hypopharynx	2	2
Pyriform sinus	1	1
Post cricoids	1	1

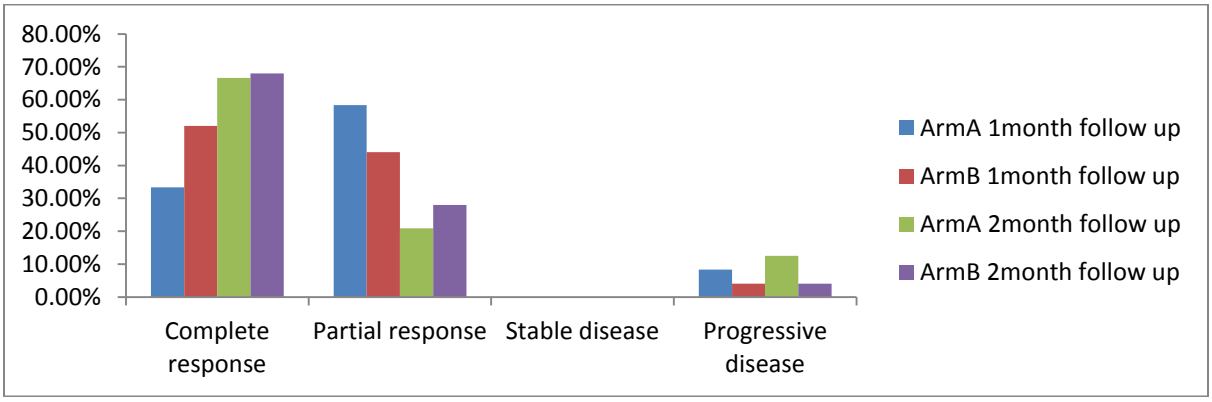

Figure 2: Response to disease after Chemo radiation

Grade 1 skin rash was observed in 33.33% patients in Arm A and 32% patients in Arm B during RT. Grade 2 skin rash was observed in 54% patients in Arm A and 60% patients in Arm B during RT. Graph 3: Skin Rash

Table 2: Side effects in treatment

Skin Rash	ArmA RT	ArmB RT	ArmA 1month	ArmB 1month	ArmA 2months	ArmB 2months
Grade1	33.33%	32.00%	33.33%	16.00%	0.00%	0.00%
Grade2	54.17%	60.00%	0.00%	0.00%	0.00%	0.00%
Grade3	12.50%	8.00%	0.00%	0.00%	0.00%	0.00%
Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.371		p=0.143			
Dysphagia						
Grade1	0.00%	4.00%	29.17%	44.00%	62.50%	20.00%
Grade2	37.50%	48.00%	45.83%	56.00%	0.00%	0.00%
Grade3	62.50%	48.00%	20.83%	0.00%	0.00%	0.00%
Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.117		p=0.028*		p=0.271	
Dry Mouth						
Grade1	91.67%	92.00%	66.67%	60.00%	37.50%	40.00%
Grade2	0.00%	0.00%	33.33%	40.00%	58.33%	52.00%
Grade3	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.008*		p=0.264		p=0.574	
Mucositis						
Grade1	0.00%	0.00%	41.67%	28.00%	62.50%	20.00%
Grade2	12.50%	52.00%	41.67%	20.00%	0.00%	0.00%
Grade3	87.50%	48.00%	0.00%	0.00%	0.00%	0.00%

Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.529		p=0.590		p=0.659	
Nausea						
Grade1	8.33%	4.00%	8.33%	28.00%	8.33%	20.00%
Grade2	33.33%	68.00%	41.67%	48.00%	33.33%	8.00%
Grade3	58.33%	28.00%	50.00%	24.00%	0.00%	0.00%
Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.803		p=0.355		p=0.319	
Vomiting						
Grade1	8.33%	24.00%	66.67%	52.00%	37.50%	12.00%
Grade2	33.33%	32.00%	12.50%	0.00%	0.00%	0.00%
Grade3	58.33%	44.00%	0.00%	0.00%	0.00%	0.00%
Grade4	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
	p=0.427		p=0.715		p=0.096	

Patients having Global health scores >50 were higher in Arm B at baseline and also at completion of RT and at 1st and 2nd month follow-up. All patients in Arm B had scores >50 by the time of 1st month follow-up.

Table 3: Global health scores and various functioning in the study

Global Health Score	**Pre RT**	**Completion of RT**	**1st month Follow up**	**2nd month Follow up**
% of patients with score greater than 50%				
Arm A	52.00%	29.17%	79.17%	83.33%
Arm B	64%	32.00%	96%	100%
Mean score				
Arm A	51.9	38.9	55.3	64.7
Arm B	55.5	41.6	65.7	70.9
	p=0.461	p=0.624	p=0.389	p=0.567
Physical Functioning				
% of patients with score greater than 50%				
Arm A	92.00%	79.17%	87.50%	96%
Arm B	100%	36.00%	60.00%	100%
Mean score				
Arm A	77.4	51.75	66.12	81.16
Arm B	72.36	41.24	56.68	78.92
	p=0.624	p=0.217	p=0.624	p=1.00
Role Functioning				
% of patients with score greater than 50%				
Arm A	92.00%	70.83%	91.67%	92%
Arm B	100%	72.00%	100%	100%
Mean score				

Arm A	73.12	57.75	71.75	82.92
Arm B	76.84	57.12	74	80
	p=0.683	p=0.775	p=0.902	p=0.967
Emotional Functioning				
% of patients with score greater than 50%				
Arm A	84.00%	83.33%	92%	95.83%
Arm B	72.00%	40%	100.00%	100%
Mean score				
Arm A	70.04	61.41	66.83	78.2
Arm B	58.72	50.2	68.48	80.6
	p=0.202	p=0.512	p=0.486	p=0.838
Cognitive Functioning				
% of patients with score greater than 50%				
Arm A	96%	91.67%	100%	100%
Arm B	100.00%	100%	100%	100%
		Mean score		
Arm A	86.48	67.5	89.04	91
Arm B	71.4	73.68	78.72	87
Social Functioning				
% of patients with score greater than 50%				
Arm A	84.00%	87.50%	91.67%	100.00%
Arm B	100.00%	52.00%	96%	100.00%
Mean score				
Arm A	69.12	65.37	79.41	82.75
Arm B	71.36	56.72	69.12	80.24
	p = 0.744	p = 0.436	p = 0.683	p = 0.838
Pain				
% of patients with score greater than 50%				
Arm A	0.00%	100%	100.00%	96%
Arm B	40.00%	92.00%	0.00%	0%
% of patients with score greater than 50%				
Arm A	31.84	71.83	65.58	62.58
Arm B	48.44	63.44	27.36	20.84
	p = 0.126	p = 0.713	p = 0.029	p = 0.305

Table 4: Various parameters in the study after treatment

Swallowing	**Pre RT**	**Completion of RT**	**1st month Follow up**	**2nd month Follow up**
% of patients with score greater than 50%				
Arm A	0%	67%	8.33%	0.00%
Arm B	12%	48%	0.00%	0%
Mean score				
Arm A	22.84	54.75	42.87	21.91
Arm B	34.6	54	19.24	8.15
	p = 0.116	p = 0.624	p = 0.106	p = 0.023*

Senses				
% of patients with score greater than 50%				
Arm A	0%	67%	8.33%	0.00%
Arm B	12%	48%	0.00%	0%
Mean score				
Arm A	20.24	42.25	25.95	16.87
Arm B	12.28	34.84	17.4	10.79
	p = 0.567	p = 0.870	p = 0.512	p = 0.061
Speech				
% of patients with score greater than 50%				
Arm A	0.00%	79%	0%	0.00%
Arm B	0.00%	52.00%	0%	0.00%
Mean score				
Arm A	31.08	59.5	28.5	17.95
Arm B	31.64	54.84	24.76	9.79
	p = 0.539	p = 0.567	p = 0.624	p = 0.935
Sexuality				
% of patients with score greater than 50%				
Arm A	0.00%	79%	0%	0.00%
Arm B	0.00%	60.00%	0%	0.00%
Mean score				
Arm A	31.52	59.62	28.37	17.66
Arm B	31.64	54.76	24.72	9.32
	p = 0.539	p = 0.567	p = 0.624	p = 0.935

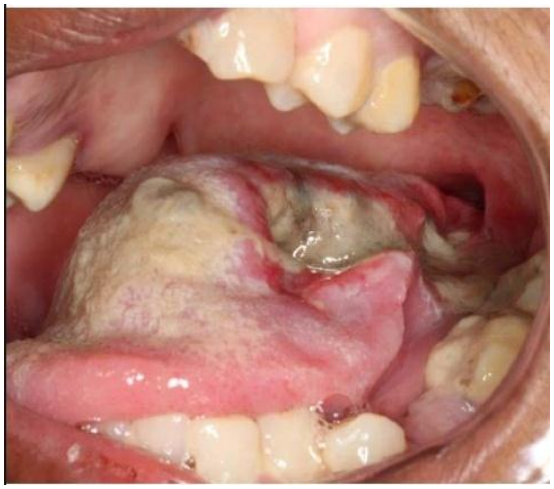

Figure 3: Patient with carcinoma tongue

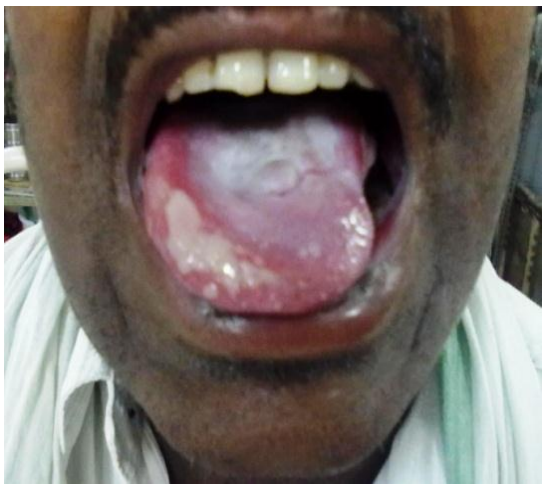

Figure 4: Grade III mucositis of carcinoma tongue

Discussion

The addition of chemotherapy to radiotherapy has become the standard of care for loco-regionally advanced head and neck cancers. Regarding the type of drugs to be combined concomitantly with radiotherapy, cisplatin alone, cisplatin or carboplatin associated with 5-FU or other poly-chemotherapy including either platin or 5-FU gave a benefit of same order of magnitude according to **MACH-NC by Pignon et al [**4].Cisplatin bolus at a dose of 100mg/m2 on days 1, 22 and 43 of RT was originally developed for use in clinical trials of induction chemotherapy and later incorporated in chemo radiotherapy regimens. Radical radiotherapy with concurrent chemotherapy utilizing high dose cisplatin (80 – 100 mg/m^2) cycled every three weekly during definitive radiotherapy is the standard followed in Western countries. In the present study patients with carcinoma of oral cavity were younger in age group which was similar to what has been reported in literature in Indian context. At present the commonest age group to get oral cavity cancer is 31 to 40 years (38.5%) and is followed by the age group of 21 to 30 years (35.4%). The habit of consumption of smokeless tobacco (gutkha) is the cause of it. It contains tobacco, betel nut, lime and flavouring agents, all of which have been proven to be carcinogenic. Tobacco related cancers account for nearly 48.2% of all cancers in Indian men and 20.1% in women. The age adjusted rates of head and neck cancers are highest in countries like France, India, Brazil, and the USA (blacks) [5]The incidence of male to female head and neck cancers in Indian population is 4:1[43] which is almost similar to our study population in which Arm A had 21 male patients and 4 female patients while Arm B had 20 male patients and 5 female patients. In India, 25% of all male cancers and 10% of all female cancers are reported to be head and neck squamous cell cancers [6] Among females the age adjusted rates of India are the highest in the world [5].

In the present study 88% of the patients had ECOG performance status of 1, while 12% of the patients had ECOG performance status of 2 in both the arms. Although medical co-morbidities consistent with age pyramid were prevalent, they were not significant enough precluding systemic chemotherapy.

In Arm A of present study 56% patients had stage III, 32% patients had stage IV A and 12% patients had stage IV B disease respectively. In Arm B 60% patients had stage III disease, 36% patients had stage IV A disease and 4% patients had stage IV B disease respectively. Head and neck cancer is a major concern in the Indian public health field as it is one of the most common types and still spreading at alarming rate. India is classified as a lower-middle-income group country by the World Bank. 90% of the oral cavity cancer patients belong to the lower or lower-middle socio-economic class and 3.6% are below the poverty line based on Pareek's classification. [7]

A number of studies have shown that a substantial fraction of patients could not receive the third planned dose of three-weekly cisplatin and suggested that a cumulative dose of 200mg/m2 might be adequate to yield the same beneficial effect

Geeta et al. in their study observed that 64% patients completed all the three cycles of chemotherapy in their three weekly arm. In their 40mg/m^2 weekly chemotherapy arm 64% patients completed 6 cycles of planned chemotherapy. 4 out of 32 patients in the weekly group received less than 5 cycles [8].

In **RTOG 9501** study, 61% of patients received all 3 planned cycles of cisplatin, 23% received 2 cycles, 13% received 1 cycle and 2% received no chemotherapy. In the **EORTC 22931** study compliance to chemotherapy also decreased according to the number of courses delivered as the first, second and third cycles were administered to 88%, 66%, and 49% patient's respectively[9]. The weekly 40mg/m^2 dose of cisplatin is thought to be more easily administered than cisplatin at a dosage of 100mg/m^2 every 3 weeks

Gupta et al. reported two-thirds(65%) of patients received >85% of planned cisplatin dose of weekly 30mg/m2 and the median number of chemotherapy cycles was 6[10].

Tsan et al. in their study reported 88.5% of patients in three weekly arm and 62.5% of those in the weekly arm received >200mg/m^2 of cisplatin in total. In their study three weekly high dose cisplatin treatment showed higher compliance [11].

However, **Ho et al.** reported that more patients received a higher cumulative dose, Although no randomized study has been performed in head and neck cancer to demonstrate the importance of dose intensity, given that an important impact on survival has been demonstrated by synchronous chemoradiation, it would suggest that maintaining dose intensity during synchronous chemotherapy will be important when treating patients [12].

In present study the arms had almost similar disease response and the p value was not significant. Response to chemo radiation depends on multiple factors including factors related to the primary tumour, patient factors, biologic factors, treatment factors. Therefore a wide variation in response rates (34% to 72%) is mentioned in literature by different authors.

Ho et al. reported 80% complete response rate and 12% partial response rate while 8% patients had progressive disease in the three-weekly arm. Relapse within the radiotherapy field was observed in 11 patients in the three-weekly group, with 4 patients relapsing distantly. In the weekly group, local relapse was observed in four patients with a further four relapsing distantly [12].

Gupta et al. reported that patients receiving >85% of the planned dose (6 or more cycles of weekly chemotherapy) had a significantly superior 5-year local control (64.5% vs 41.8%); loco-regional control (54.4% vs 26.8%) and disease free survival (49.6% vs 25.8%) as compared to lesser dose intensity (1-5 cycles of chemotherapy)[10]

Maqbool et al. reported response rates in 45 patients treated with 6 cycles of 40mg/m2 weekly cisplatin with 66-70Gy radiation. They observed a complete response in 26 patients (57.7%) and partial response in 14(31.1%) and stable disease in patients (11.1%)[13].

Homma et al. showed a complete response of 98.1% and a partial response rate of 1.9% with 58.5% patients receiving > 200mg/m2 of weekly cisplatin [14].

In the present study grade skin rash was observed in 33.33% patients in Arm A and 32% patients in Arm B during RT. Grade 2 skin rash was observed in 54% patients in Arm A and 60% patients in Arm B during RT. Grade 3 skin reaction was observed in 12.5% patients in Arm A and 8 % patients in Arm B. At 1 month post RT 33% patients in Arm A and 16% patients in Arm B had grade 1 skin reaction. None of the patients in either arms had grade 2 or 3 skin reaction. At 2nd month of follow up skin reactions were not seen in any of the patients. The differences were however statistically insignificant.

During RT 37.5% patients had Grade 2 dysphagia and 62.5% patients had Garde 3 dysphagia in Arm A while 4% patients had Grade 1, 48% patients had Grade 2 and 48% patients had Grade 3 dysphagia in Arm B. At 1 month of RT completion 29.17% patients had Grade 1 dysphagia, 45.83% patients had Grade 2 dysphagia and 20.83% patients had Grade 3 dysphagia in Arm A while 44% patients had Grade 1 and 56% patients had Grade 2 dysphagia in Arm B which was statistically significant. After 2 months of RT completion 62.5% patients had Grade 1 dysphagia in Arm A while 20% patients had Grade 1 dysphagia in Arm B.

In the current study 91.67% patients in Arm A and 92% patients in Arm B had Grade 1 dry mouth. At 1 month of RT completion 66.67% patients had Grade 1 dry mouth and 33.33% patients had Grade 2 dry mouth in Arm A and 60% patients had Grade 1 dry mouth and 40% patients had Grade 2 dry mouth in Arm B. At 2 months of RT completion 37.5% patients had Grade 1 dry mouth and 58.33% patients had Grade 2 dry mouth in Arm A and 40% patients had Grade 1 dry mouth and 52% patients had Grade 2 dry mouth in Arm B respectively. The p value was not significant.

The incidence and severity of mucositis shows its impact on pain, dysphagia, feeding tube placement, hospitalization, treatment modification or interruptions, weight loss and tumour response and quality of life. The present study showed that 12.5% patients in Arm A had Grade 2 mucositis and 87.5% patients had Grade 3 mucositis in Arm A whereas 52% patients had Grade 2 mucositis and 48% patients had Grade 3 mucositis in Arm B .At 1 month of RT completion 42% patients had Grade 1 mucositis and 42% patients had Grade 2 mucositis in Arm A and 28% patients had Grade 1 mucositis and 20% patients had Grade 2 mucositis in Arm B. At 2 months of RT completion 63% patients had Grade 1 mucositis in Arm A and 20% patients in Arm B had Grade 1 mucositis. Thus arm A patients had higher rates of severe mucositis but the results were statistically insignificant.

8.33% patients had Grade 1 nausea, 33.33% patients had Grade 2 nausea and 58% patients had Grade 3 nausea in Arm A whereas 4% patients had Grade1, 68% patients had Grade 2 and 28% patients had Grade 3nausea in Arm B respectively. At 1 month of RT completion 8.33% patients had Grade1, 42% patients had Grade 2 and 50% patients had Grade 3 nausea in Arm A whereas 28% patients had Grade1, 48% patients had Grade 2 and 24% patients had Grade 3 nausea in Arm B respectively. After 2 months of RT 8.3% patients had Grade 1 nausea and 33.3% patients had Grade 2 nausea in Arm A whereas 20% patients had Grade 1 and 8% patients had Grade 2 nausea in Arm B respectively.

In the present study,8% patients had Grade 1 vomitting, 33.33% patients had Grade 2 vomitting and 58% patients had Grade 3 vomitting in Arm A whereas 24% patients had Grade 1, 32% patients had Grade 2 and 44% patients had Grade 3 vomitting in Arm B respectively. At 1 month of RT completion 66.67% patients had Grade1, 12.5% patients had Grade 2 vomiting in Arm A whereas 52% patients had Grade1 vomiting in Arm B respectively. After 2 months of RT 38% patients had Grade 1 vomiting in Arm A whereas 12% patients had Grade 1 vomiting in Arm B respectively. However, the resulting difference was not statistically significant.

Haematological toxicity in the form of decreased haemoglobin was Grade 1 in 75% patients and Grade 2 in 8.3% patients in Arm A whereas grade 1 was in 80% patients and Grade 2 was in 8% patients in Arm B during RT. 83.33% patients in Arm A and 80% patients in Arm B had Grade 1 after 1 month as well as after 2

months of RT completion. The difference was not statistically significant.

Drop in total leukocyte count was observed only during RT in both the arms. Grade 1 leukopenia was observed in 32% patients, Grade 2 was observed in 16% patients in Arm A whereas 28% patients in Arm B had Grade 1. One patient died due to myelosuppression after one cycle of chemotherapy in Arm A.

Platelet counts and renal parameters were normal for all patients during and after RT on subsequent follow-up.

Gupta et al. reported with 30mg/m2 weekly cisplatin RTOG acute grade 3 or worse mucositis and dermatitis was seen in 29.2% and 34.8% patients respectively, most of the time in patients receiving more intense treatment i.e. doses >66Gy and 6 or more cycles of chemotherapy. CTC grade III emesis occurred in 3.4% patients and CTC grade 3 leukopenia was 5.7%. No episodes of febrile neutropenia were recorded. Overall the regimen was well tolerated with acceptable acute toxicity. They proposed that since the toxicity of weekly cisplatin in the 30mg/m2 dose range is substantially lower than the high dose three weekly schedules, combining weekly chemotherapy with altered fractionation may be more acceptable to the practicing oncologist [10].

Huguenin et al. employed 2 cycles of cisplatin which was divided into 5 doses of cisplatin 20mg/m2 given daily. The results of their study suggested less systemic toxicity and mucositis without compromising local control and overall survival [15].

Ho et al. reported that haemoglobin dropped by a mean of 3.1g/dl after chemo radiation in 3 weekly arm and a mean of 3.3g/dl for patients in the weekly arm. A proportionally higher number of patients having grade 3 neutropenia on the three weely regime experienced neutropenic fever (83% vs 40%) which was not significant. Moist desquamation of skin was 56% in 3 weekly and 26% in the weekly arm. Renal, gastrointestinal and neurological toxicity was similar in both arms. They concluded that delivering weekly cisplatin at a dose of 40mg/m2 in the outpatient department appears to have similar toxicity and efficacy to a 3 weekly concurrent chemo radiation regime but is less subject to delays in treatment and reductions in dose intensity due to administrative failures[12].

Tsan et al.observed that overall toxicity was significantly greater for patients in weekly arm compared to three weekly arm .All grade 4 toxicities were observed in the weekly arm. Grade 3 mucositis was seen in 38.5% in three weekly arm and 75% patients in weekly arm. They concluded that three weekly high dose cisplatin showed high compliance, low acute toxicity and better physical well being compared to weekly low dose cisplatin[11].

In the Japanese study done by **Homma et al .**with weekly cisplatin, it was observed that 39.6% patients developed Grade III and IV mucositis and 26.4% patients developed grade 3 or greater leukopenia.. They concluded that weekly cisplatin could be easier to manage than three-weekly cisplatin because patients could be more regularly managed for toxicity, and the schedule can be changed before the effects become severe, based on the patient's condition. Because the dose delivered in each cycle is smaller, the toxicity is reduced thus recommending it to be a suitable alternative to three-weekly high dose cisplatin concurrent with radiation [14].

A study from Brazil done by **Herchenhorn D et al.** concluded "our experience confirmed the difficulty of administering combined therapy with cisplatin 100mg/m2 and radiation to patients with locally advanced larynx and oropharynx cancer, even with selection of performance status 0 and 1 patients; the toxicity is very high, and the results are worst with more advanced disease (stage IV b). This combination should be considered the standard treatment for organ preservation only in institutions with experience in treating the disease and with a complete multi-disciplinary team [16].

In the present study, baseline pre-treatment QOL was measured in both the arms and compared for any difference in initial scores. The impact of the treatment on the patient QOL was evaluated by comparing the QOL scores at baseline, completion of RT, 1st month and 2nd month after completion of treatment. The analysis of QOL in both the arms showed that patients in both the arms had decreased QOL during the chemo radiotherapy treatment and the decrease was more in the Arm A, and the QOL scores reached baseline in the Arm B compared to Arm A for most of the function scales and symptom scales at 1 month follow up, and the same trend continued even at 2nd month follow up. However there was no statistical difference for most of the parameters except pain at 1st month follow-up and swallowing at 2nd month follow up. This was due to small sample size.

Tsan et al. conducted one of the first studies to compare health related quality of life between the weekly low dose and 3 weekly high dose cisplatin CCRT. Their results indicated that physical wellbeing (PWB) of patients receiving weekly chemotherapy decreased more significantly than 3-weekly group. However social wellbeing scores were lower in three weekly arm compared to the weekly arm which was hard to explain clinically [11].

A recent study by **Sendilnathan et al** was published in the recent **2015 ASCO Annual Meeting**. They reported their observation of Quality of life (QOL) as a predictor of clinical outcome in patients with head and neck cancer using EORTC C-30 and EORTC H&N-35 questionnaire. They observed that functional outcome (FX) and general symptoms (SX) scales along with nutrition, social contact and total EORTC-35 score worsened by 3 months. Global Health Status (GHX) worsened by 6 months. Early recurrences correlated with worse SX scale, FX, or nutrition scores at baseline or GHX at 6 months. Poor nutrition, poor eating skills, and low total EORTC-35 score also predicted early recurrence. Higher mortality also correlated with worse baseline SX scale, nutrition, and overall EORTC 30 measure [17].

Conclusion

Though the current standard of care for locally advanced head and neck cancer is concurrent chemo radiation with high dose cisplatin given every three weekly at a dose of 100mg/m^2, it has a very poor patient compliance owing to the chemotherapy related complications, severe acute toxicity and persistent late toxicity leading to poor patients' quality of life. On the other hand the concurrent chemoradiotherapy with weekly Cisplatin has given similar tumor control and a better patient's compliance with a relatively good quality of life. Therefore in our setup, where patients are nutritionally compromised and economically backward, radical radiation with weekly concurrent cisplatin is a viable and an effective treatment option. However long term data is needed regarding late toxicities, local recurrence rates and survival rates with a larger sample size and randomization.

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