http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i2.82

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

3 Arm comparisons to evaluate the role of concurrent chemoradiation in locally advanced squamous cell carcinoma of head & neck region

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Abstract
Background: *In locally advanced squamous cell carcinoma of head and neck regionthe most widely used drug in concurrent chemoradiation is cisplatin but the optimal regimen of cisplatin is still not defined. The aim of this study was to determine the efficacy of CCRT with weekly cisplatin vs 3 weekly cisplatin and 5 fluorouracil and to compare it with conventional radiotherapy only treatment. We also evaluated the toxicity of the 3 arms.*
Material and Method: *Outcome data of 60 patients of histologically proven squamous cell carcinoma of head and neck treated between 2007-2010 was analysed. 20 patients had received only conventional RT; 20 patients had received conventional RT along with weekly cisplatin and 20 patients had received conventional RT along with cisplatin & 5-FU on D1-D4 &D22-25 of RT.*
Results: *At 5 years overall survival was 25% in the RT only arm, 50% in the weekly cisplatin arm and 35% in the 3 weekly cisplatin and 5-FU arm. The DFS was 20%, 40% &25% respectively in the 3 arms.*
Conclusion: *Patients treated with weekly cisplatin CCRT had a higher 5 year OS and DFS as compared to those treated with 3 weekly cisplatin & 5FU CCRT or RT alone.*

Introduction

Head and neck cancers are a heterogenous group of cancers and worldwide approximately 600,000 patients are afflicted.[1] In India over 200,000 new cases of Head & Neck cancers and over 100,000 deaths occur each year.[2] Majority of the patients are in the 50-70 years age group.[1] Traditionally surgery and radiotherapy either alone for early stage disease or in combination for locoregionally advanced disease had been considered curative for H & N cancers.[3,4] Optimal treatment for locally advanced head & neck cancer remains a challenge and concurrent chemoradiation is now considered the standard of care for nonsurgical treatment of these patients.[5-8]

A meta-analysis of >17,346 patients of 93 trials conducted from 1965-2000 (meta-analysis of chemotherapy on Head and Neck cancer [MACH-NC]) demonstrated that the use of radiotherapy and concurrent chemotherapy (CCRT) resulted in a 19% reduction in the risk of death and an overall 6.5% improvement in the 5 year survival compared to treatment with RT alone.[9] The most widely used chemotherapy drug is cisplatin but the optimal regimen of cisplatin is still not defined. The most widely used concurrent chemoradiation schedule uses high dose bolus cisplatin 100mg/m^2 every 3 weeks in combination with standard radiotherapy.[9-13] Cisplatin has also been used concurrently with radiation in other schedules – low dose daily, few days per week, or weekly schedule.[14-17]

There exists considerable difference in choosing the optimal chemoradiation schedule due to heterogeneity of study designs and different ways of combining CT and RT. This retrospective study attempts to analyse patients treated with two different regimens of cisplatin based CCRT and to compare their results with RT alone. The aim was to see OS and DFS at 5 year. We also analysed the acute and late toxicities in the 3 arms.

Material and Methods

Patients

Patients with head and neck cancer who were treated with only RT, RT with weekly cisplatin and RT with 3 weekly cisplatin and 5-FU from December 2007to December 2010 were retrospectively identified from our department data base. 20 patients were identified in each of the 3 arms. Inclusion criteria were histologically proven squamous cell carcinoma of, locally advanced (stage III & IV) where surgery not feasible / refused, no previous oncological therapy other than biopsy, KPS 60-100, no significant co-morbidity that would preclude the use of CT and RT, age greater than 20 years, normal hematological, renal and liver function tests and no previous cancer within last 5 years or a second primary. Exclusion criteria were patients with distant metastasis, recurrent tumors, second primary neoplasm, paranasal sinusand nasopharyngeal cancer.

Treatment

Patients in arm A received only conventional RT. Patients in arm B received Inj cisplatin 40mg/m^2 weekly along with conventional RT. Patients in arm C received Inj cisplatin 20mg/m^2&Inj 5-FU 1gm/m^2 on days 1-4and days 22-25 of conventional RT. The total dose of RT was 60-70 Gy at 2 Gyper fraction, 5 fractions/week in all the 3 arms. Most of the patients were treated with B/L opposing portals and a few with 3 field technique (B/L opposing portals for primary and upper neck and a low anterior neck field matched to the upper field). Field reduction was done at 44Gy to spare the spinal cord. All patients were treated with Cobalt-60 machine.

Assessment of Toxicity and Response

All the patients were monitored weekly to evaluate the development of acute toxicities like nausea, vomiting, mucositis, skin rash and neutropenia. Blood counts, RFT and LFT were performed weekly during RT. Treatment toxicities were graded according to the RTOG guidelines. Patients whose performance status, LFT, RFT or CBC deteriorated during RT were considered unfit for CT. In these patients that particular cycle of CT was omitted and no dose reductions were planned.

Primary and nodal response was assessed clinically every week during treatment and after one month of completion of treatment. Thereafter patients were followed up monthly for the first year, once in 3 months in the second year, once in 6 months in the third to fifth year and then annually. In follow up, detailed clinical examination was done to see the result of the treatment at the disease site and lymph node region, toxicities and detection of any distant metastasis. Treatment response was assessed by the RECIST criteria. If there was any suspicion of recurrence, patient was sent for evaluation and

biopsy. Patients who had completed the planned treatment but were not coming for follow up were contacted telephonically.

Data Analysis

Analysis was performed using SPSS software. The study was approved by our institutional ethics committee and all the patients provided informed consent.

Results

Patient Characteristics

Table 1 depicts the characteristics of the patients. Overall 80% of the patients were males and the median age at presentation was 57 years in arm A, 56 years in arm B and 55.5 years in arm C, with a range from 35-72 years. Overall the most common primary site was oropharynx (31.6%) followed by larynx (30%) hypopharynx (21.6%) and oral cavity (16.67%) In arm A, 12 (60%) patients were in stage III & 8(40%) in stage IV. In arm B 9(45%) were in stage III and 11(55%) in stage IV where as in arm C 10pts were in stage III & IV each (50%).

Analysis of Overall Tumor Response and Survival at 5 Years

All patients completed the planned treatment. Patients were followed for 30-66 months with a median follow up of 42 months. At the first follow up, after one month of completion of treatment, complete response was seen in 12 patients (60%) in arm A, 17(85%) in arm B and 15(75%) in arm C. Partial response was seen in 6 patients (30%) in arm A, 3(15%) in arm B and 5(25%) in arm C. Stable disease was seen in 2 patients (10%) in arm A. As a measure of efficacy of treatment the analysis was limited to first failures only. Data was analysed till June 2013. At that time, the projected overall survival at 5 years was 25% in Arm A, 50% in Arm B and 35% in Arm C. The projected DFS at 5 years was 20% in arm A, 40% in arm B and 25% in arm C.

Toxicity Analysis

Acute toxicity: Median time of onset of symptoms of acute toxicities was 18 days in arm A, 16 days in arm B and 12 days in arm C. Most of the patients in arm A suffered Grade I/II toxicities where as in CCRT arms Grade III/IV toxicities were more prevalent. Majority of the patients in arm A experienced Grade I/II skin toxicity. In arm B , Grade III and IV skin toxicity was seen in 50% & 20% of the patients. Patients in arm C experienced more severe skin toxicity with 45% Grade III and 30% Grade IV skin reactions. Grade III mucositis was 60% in arm B &50% in arm C whereas Grade IV mucositis was more common in arm C (35%) as compared to arm B (15%). Majority of the patients in arm A experienced Grade I & II mucosal toxicity. Nausea and vomiting was mild to moderate in arm A Grade II vomiting was 60% in arm B & 50% in arm C whereas Grade III vomiting was seen in 20% of patients in arm B and 35% in arm C. Dysphagia was mostly Grade I/II in arm A. Both the arms B and C experienced Grade II dysphagia in 50% patients. Grade III dysphagia was higher in arm C as compared to arm B (45% vs 30%). Neutropenia was experienced by 2 patients (10%) in arm B and one patient (5%) in arm C.High incidence of mucositis and dysphagia in the concurrent arms led to a more frequent use of NG tube feeding in the CCRT arms as compared to the RT only arm. NG tube insertion was done in 11 patients (55%) in arm B and 14 patients (70%) in arm C as compared to only one patient (5%) in arm A.

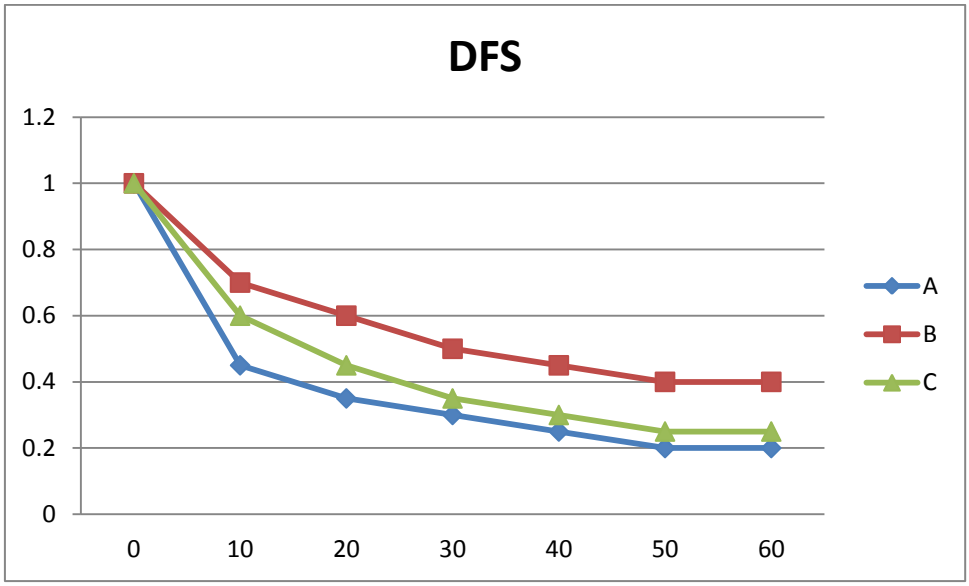
Late Toxicity: The most prominent late toxicity seen at the time of analysis was xerostomia. Out of the 5 patients alive in arm A, 3 had Grade I& 1 had II toxicity. Of the 10 patients alive in arm B, 6 had Grade I and 4 had II toxicity. Out of the 7 patients alive in arm C , 4 had Grade I & 3 had II toxicity. Subcutaneous fibroses was seen in 2 patients in arm A, 4 patients in arm B and 3 patients in arm C. Trismus was present in 1 patient in arm A and 2 in arm B and C each. Significant hearing lost was seen in 3 patients in arm B and 2 patients in arm C. Persistent dysphagia was seen in 2 patients in arms B and C each.

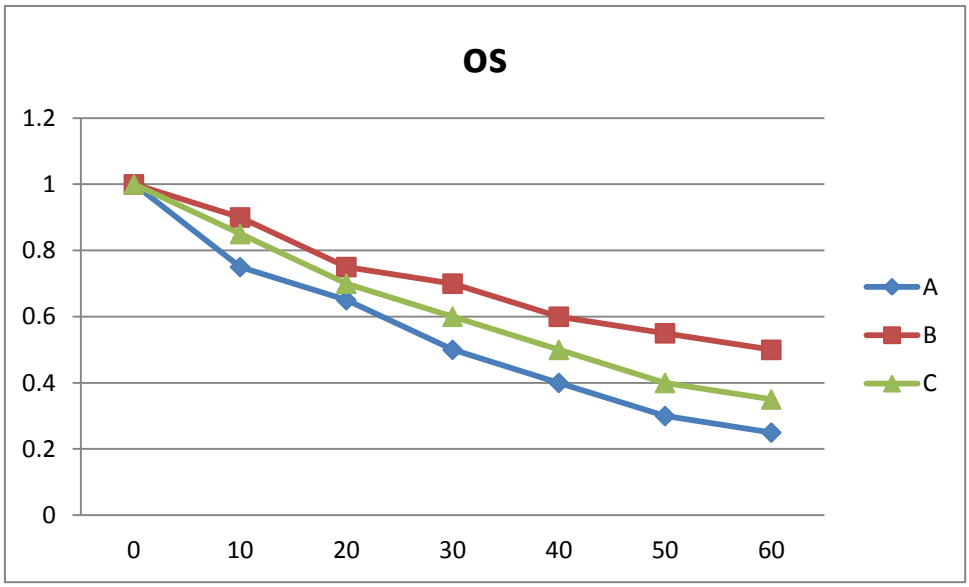
Table-1 Patient Characteristics

S. No.		RT only		RT+ Wkly Cisplatin		RT+ 3 wkly CDD+ 5-FU		Total	
		No.	%	No.	%	No.	%	No.	%
1	Number of patients	20		20		20		60	
2	Male:female	16:4	80/20	15:5	75/25	17:3	85/15	48/12	80/20
3	Median age (years)	57		56		55			
4	Disease location								
	Oropharynx	6	30	6	30	7	35	19	31.6
	Larynx	7	35	6	30	5	25	18	30
	Hypopharynx	4	20	4	20	5	25	13	21.6
	Oral cavity	3	15	4	20	3	15	10	16.7
5	Stage								
	III	12	60	9	45	10	50	29	48.3
	IV	8	40	11	55	10	50	31	51.7

Table - 2 Results

S. No.		RT only		RT + Weekly Cisplatin		RT + 3 Weekly Cisplatin +5 FU	
		No.	%	No.	%	No.	%
1	CR	12	60	17	85	15	75
2	PR	6	30	3	15	5	25
3	SD	2	10	0	0	0	0
4	Median duration of Followup						
5	OSat 5 years	5	25	10	50	7	35
6	DFS at 5 year	4	20	8	40	5	25
	Acute toxicities						
7	Mucositis Grade						
	I	10	50	0	0	0	0
	II	8	40	5	25	3	15
	III	2	10	12	60	10	50
	IV	0	0	3	15	7	35
8	Dermatitis						
	I	12	60	2	10	0	0
	II	8	40	4	20	5	25
	III	0	0	10	50	9	45
	IV	0	0	4	20	6	30
9	Vomiting						
	0	10	50	0	0	0	0
	I	6	30	4	20	3	15
	II	4	20	12	60	10	50
	III	0	0	4	20	7	35
10	Dysphagia						
	I	10	50	4	20	1	5
	II	9	45	10	50	10	50
	III	1	5	6	30	9	45
11	Neutropenia	0		2	10	1	5
	Late toxicity						
12	Salivary gland						
	0	1		0		0	
	I	3		6		4	
	II	1		4		3	
13	Subcutaneous fibrosis						
	Present	2		4		3	
	Absent	3		6		4	
14	Trismus	1		2		2	
15	Hearing loss	0		3		2	
16	Dysphagia	0		2		2	





Discussion

The updated meta analysis of CT in Head and Neck cancer (MACH-NC) confirmed the original findings of 4% OS withCCRT.[6,7,9] The study also showed a relative 19% improvement in survival for concomitant therapy translating into an 8% absolute benefit in OS with platinum based regimens. However there is confusion regarding the most appropriate CCRT regimen because the data that have been published are very heterogenous regarding the CT drug and its schedule. A randomized trial from Cleveland clinic assigned patients to receive 66 to 72 Gy ± 2 days of synchronous cisplatin (20 mg/m^2/day×4) and infusional 5-FU (1000 mg/m^2/day×4) during week 1 and 4 of RT. Surgery was planned for patient with residual or recurrent local/nodal disease. Projections for 5 year overall survival with primary site preservation were 34% Vs 42% (p=0.004) and for local control without surgical resection were 45% Vs 77% (p<0.001).[18]In arm C of our study, the 5 year DFS was 25% vs 20% in arm A & 5 year OS was 35% Vs 25%.In a large single centre experience of weekly cisplatin 30 mg/m^2 concurrently with RT of 70 Gy at 2 Gyperfraction, 5 fractions/week. Gupta et al. reported a 5 year DFS of 43%[19]. In arm B of our study, the 5 year DFS was 40% and OS was 50%.

Our study used 2 different CT regimens in the CCRT arms and compared their results with an only conventional RT arm. The CR seen at 1 month after completion of treatment was 85% in

the weekly cisplatin arm (arm B), 75% in the 3 weekly cisplatin and 5-FU arm (arm C) and 60% in the RT only arm (arm A).Acute toxicities were considerably higher in the two CCRT arms as compared to the RT only arm and were similar to the acute radiation morbidity seen in CCRT arm of RTOG 91-11 trial and trial by Forastiere.[20] Grade III/IV mucositis was significantly higher in arm C (85%) as compared to arm B (75%).

Arm A completed the planned treatment without any interruption. In arm B, 15 patients (75%) completed 6 cycles of the planned weekly chemotherapy, 3 patients (15%) received 5 cycles and 2 (10%) received only 4 cycles of weekly chemotherapy. In arm C, all patients (100%) received at least one cycle of chemotherapy starting from D1 of RT and 15 (75%) completed the planned 2 courses of the 3 weekly chemotherapy. Chemotherapy in these patients had to be omitted in case of deteriorating performance status, severe mucosal or skin toxicity or neutropenia. Patients in arm B received higher cumulative dose of cisplatin (90% receiving atleast 200 mg/m^2) as compared to arm C (75% receiving only 160 mg/m^2 cisplatin and 8 gm/m^2 5-FU). Higher CR seen in arm B than arm C may be due to higher chemotherapy dose received by patients in arm B due to lower toxicity and better compliance as compared to arm C. The overall survival at 5 years was 25% in arm A, 50% in arm B and 35% in arm C which was not statistically significant. DFS at 5 years was 20% in arm A, 40% in arm B and 25% in arm C and the difference was not statistically significant. Treatment interruption in arm B was less than 1 week and was seen in 5 patients. In arm C, treatment interruption was less than one week in 6 patients and more than one week in 2 patients. More patients were hospitalized for conservative management of acute toxicities in arm C as compared to arm B (10 patients Vs 7 patients). No patient in arm A was hospitalized for toxicity management. The incidence of late toxicities like xerostomia and subcutaneous fibrosis were almost similar in the three arms. This was as expected because these toxicities depend on radiation dose which was similar in the 3 arms. Hearing loss was seen only in the CCRT arms probably due to the ototoxic effect of cisplatin.

Conclusion

In this study the OS and DFS at 5 years is superior in the arm receiving weekly cisplatin as compared to the arm receiving 3 weekly cisplatin based regime & RT only arm. However, the difference in overall survival and disease free survival between the three arms was found to be not statistically significant; the number of patients in each arm were only 20. Use of prospective randomized trial is warranted in this setting. The weekly cisplatin based CCRT is a tolerable and effective regimen for treating locally advanced squamous cell carcinoma of head & neck region. The limitation of this study is that it is a retrospective study.

Acknowledgement

We would like to thank our patients and the staff of Dept. of Radiotherapy for their support in completing this study.

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