ORIGINAL RESEARCH PAPER
Volume-9 | Issue-4 | April-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TO STUDY CONCURRENT CHEMORADIATION COMPARING BY CISPLATIN 20 MG/M2 5 DAYS EVERY FOUR WEEKLY VERSUS STANDARD 100 MG/M2 THREE WEEKLY IN LOCALLY ADVANCED HEAD AND NECK CANCER (LAHNC) PATIENTS.

Medical Science

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ABSTRACT

Background- Due to less study in concurrent chemoradiation schedule we conducted a study concurrent chemoradiation comparing by cisplatin 20 mg/m2 5 days every four weekly versus standard 100 mg/m2 three weekly in locally advanced head and neck cancer (LAHNC) patients. **Methods-** Hospital based prospective study conducted at Department of Radiation Oncology, S.M.S Medical College and attached group of hospital, Jaipur, Rajasthan. Response evaluation was done after 3 months of completion of treatment based on clinical examination and contrast enhanced CT scan of head and neck findings in each patient. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumor at primary site and or nodal area. **Results-**The clinical response rates obtained after 6 months of treatment follow up revealed that complete response (CR) was achieved in 25 patients (71.43%) in the Study group and 22 patients (66.67%) in the Control group. The partial response (PR) rates were 7 patients (20%) in Study group and 6 patients (18.18%) in Control group. Overall response rate (OR = CR + PR) was 91.43% in the Study group and 84.85% in the Control group. **Conclusion-**We conclude that 20 mg/m2 of cisplatin for 5 days every four weeks can be safely used with concurrent radiation in locally advanced HNSCC without compromising efficacy.

KEYWORDS

Cisplastin, Head neck tumor, Response

INTRODUCTION

Head and neck cancers include a heterogeneous group of malignant tumors arising in all structures cephalad to the clavicles, except for the brain, spinal cord, base of the skull, and usually the skin. A meaningful understanding of these malignant tumors requires anatomic separation into those cancers arising in the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, nasal fossa, paranasal sinuses, thyroid and salivary glands, and vermilion surfaces.1

Worldwide, more than 0.8million patients are diagnosed with squamous cell carcinoma of the head and neck (SCCHN) yearly, accounting for 4.6% of all cancers. Two-thirds of the SCCHN are in a loco-regionally advanced stage at diagnosis.2 In India, Head and Neck Carcinomas constitute the most common malignancy amongst men and 14.3% overall (GLOBOCAN 2018)2,3. Head and neck malignancies constitute approximately 16.70% of all cancers in our department.

Due to limited study in our region we conducted a study concurrent chemoradiation comparing by cisplatin 20 mg/m2 5 days every four weekly versus standard 100 mg/m2 three weekly in locally advanced head and neck cancer (LAHNC) patients.

MATERIAL & METHODS

Study area:
Department of Radiation Oncology, S.M.S Medical College and attached group of hospital, Jaipur, Rajasthan.

Study period:
The recruitment of patients was started after approval of research review board and institutional ethical committee from June 2018 to May 2019 and thereafter 2 months period taken for analysis of collected data.

Study type and design:
Hospital based quantitative prospective study.

Study universe:
Patients of locally advanced squamous cell carcinoma of the head and neck (histopathologically confirmed squamous cell carcinoma) attending Department of Radiation Oncology, S.M.S Hospital, Jaipur. The cases were randomly distributed among 4 weekly Cisplatin 20mg/m2 on five days group and 3-weekly cisplatin 100mg/m2 group.

Sample size:
Sample size was calculated as per seed article on minimum detectable difference of mean 18 (33 and 15), SD 26, alpha error 0.5 and 80% of study power is 33 patients in each group. Assuming 10% attrition, total 37 patients were included in each group of study.

Study Design:
Hospital based prospective, interventional, randomized, comparative study.

Method of randomization:
Chit box method with replacement.

Assessment of tumour response:
Response evaluation was done after 3 months of completion of treatment based on clinical examination and contrast enhanced CT scan of head and neck findings in each patient. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumor at primary site and or nodal area. Then patients were categorized as per RECIST Criteria (Response Evaluation Criteria In Solid Tumours).

INCLUSION CRITERIA

- Stage III to IVB histopathologically proven head and neck squamous cell carcinoma.
- Age 18-70 years.
- Either sex.
- ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2.
- Patients willing to give written informed consent.
- Inoperable disease.
- Patient fit to receive concurrent chemoradiotherapy with following parameters :
- Haemoglobin ≥9 gm%
- Absolute Neutrophil count > 1,500/uL.
- Platelet count >1,00,000/uL.
- Serum Creatinine level < 1.4mg/dl.
- Serum Bilirubin < 2 mg%.

EXCLUSION CRITERIA

- Head and neck malignancies with adenocarcinoma, mucoepidermid carcinoma, carcinosarcoma, soft tissue sarcomas, adenoid cystic carcinoma, lymphoma, skin malignancy and

thyroid malignancy.
- History of previous treatment with any of the following modalities -surgery, radiotherapy, chemotherapy for head and neck malignancies.
- Distant metastases.
- Any uncontrolled intercurrent co-morbidity.
- Double malignancy.

PATIENT EVALUATION
- History and physical examination
- Histopathological examination
- CBC, kidney and liver function tests.
- HIV/HBsAg/HCV
- Chest radiograph
- Abdominal ultrasound
- Complete ENT evaluation including FOL
- CECT/MRI of head and neck

SELECTION OF PATIENTS
- A total of 74 locally advanced stages III to IVB LASCCHN fulfilling the eligibility criteria will be selected.
- Patients will be randomly assigned to treatment groups:
- Group A- Study arm
- Group B- Control arm

CHEMO RADIATION SCHEDULE
- Study arm: Patients were given cisplatin 20 mg/m2 on five days every four weeks with conventional radiotherapy.
- Control arm: Patients were given cisplatin 100 mg/m2 IV infusion every 3 weeks with conventional radiotherapy.

RADIATION TECHNIQUE
- 66Gy in 33# (200cGy/fraction 5days in a week for $6\frac{1}{2}$ weeks) with conventional cobalt-60 external beam radiotherapy.

STATISTICAL ANALYSIS
Quantitative data will be expressed in means with standard deviation and qualitative data will be expressed in percentage proportions. Significance of difference in means of two groups will be inferred with unpaired T test. Signification of difference in means at various follow up period will be inferred with repeated ANOVA test. Significance of difference in proportion in two groups will be inferred with Chi-square test. For significance P value less than 0.05 will be considered as significance.

All patients were examined once weekly during the treatment. Heamogram and biochemical investigation were done and noted before giving chemotherapy.

The clinical appearance of the primary tumor at the initiation of treatment was noted. The regression of primary tumor during the treatment assessed and noted biweekly. Any delay causing treatment interruption was noted and necessary gap correction for radiotherapy done. Chemotherapy was withheld during radiotherapy interruptions. Radiotherapy was planned to be continued in spite of chemotherapy being discontinued due to chemotherapy related toxicities.

Patient completing the complete schedule of radiotherapy irrespective of the delay and receiving minimum 2 cycles ofcisplatin 20 mg/m2 on five days every four weeks and minimum 3cycles of cisplatin 100 mg/m2 IV infusion every 3 weeks was evaluated for response and follow up.

The results of study group was analyzed & compared with control group in terms of various aspects like compliance, side effects, tumor response, & local disease status. The data thus collected were analyzed by using Chi-square test for correlation.

RESULTS
Table No. : 1. Socio-demographic variable

	Study arm	Control arm	p-VALUE
Age (Mean±SD)	54.54±9.442	54.46±10.702	0.856
Sex (M:F)	34:3	32:5	0.702

Population in the study age ranges from 27-70 years.

Table No. : 2. Primary Site Of Disease

Primary site	Study arm		Control arm		p-value
	No.	%	No.	%	
oral cavity	8	21.62	5	13.51	Chi-square = 0.888 p = 0.926 (NS)
oropharynx	18	48.65	20	54.05	
Hypopharynx	5	13.51	6	16.22	
Larynx	6	16.22	6	16.22	
Total	37	100	37	100	

More than 50% of patients were of oropharyngeal region.

Table No. : 3. Histopathological Grade

Histopathological grade	Study arm		Control arm		p-Value
	No	%	No	%	
G1	12	32.43	9	24.32	Chi-square = 0.900 p = 0.637 (NS)
G2	19	51.35	23	62.16	
G3	6	16.22	5	13.51	
Total	37	100	37	100	

Majority of patients had Grade 2 histology.

Table No :4

AJCC Stage	Study Arm		Control Arm		p-Value
	No	%	No	%	
III	7	18.92	12	32.43	Chi-square = 1.871 P =0.392(NS)
IVA	25	67.57	20	54.05	
IVB	5	13.51	5	13.51	
Total	37	100	37	100	

Majority of patients had AJCC Stage 1V.

Table No :5.treatment Response

Response		Study Arm		Control arm		p-value
		No.	%	No.	%	1.000 NS
Response at the End Of the Treatment	CR	23	65.71	20	60.61	
	PR	9	25.71	8	24.24	
	PD	1	2.86	2	6.06	
	SD	2	5.71	3	9.09	
follow up at 3 months	CR	25	71.43	22	66.67	0.307 NS
	PR	7	20	6	18.18	
	PD	1	28.57	2	6.06	
	SD	2	5.71	3	9.09	
at 6 months	CR	25	71.43	22	66.67	
	PR	7	20	6	18.18	
	PD	1	28.57	2	6.06	
	SD	2	5.71	3	9.09	

Overall response in study group 91.43% and in control group was in 84.85% at 6 months of follow-up.

DISCUSSION
The vital importance of concurrent chemo-radiation as compared to surgery or surgery + radiotherapy or induction chemotherapy followed by radiotherapy or even hyper-fractionated radiotherapy has been proved by various randomized trials in the literature. It has become increasingly clear that use of concurrent chemotherapy with radiation contributes to improved loco-regional control and prolongs survival in locally advanced HNSCC.

This study was intended to compare 20 mg/m2 of cisplatin given for 5 days every four weeks to the standard three weekly approaches of 100 mg/m2 of cisplatin every three weeks with respect to treatment outcomes in terms of toxicity profile and locoregional control (LRC). Minimum cumulative dose of cisplatin accepted for CTRT of head and neck cancer was fulfilled in this study group.

The clinical response rates obtained after 6 months of treatment follow up revealed that complete response (CR) was achieved in 25 patients (71.43%) in the Study group and 22 patients (66.67%) in the Control group. The partial response (PR) rates were 7 patients (20%) in Study group and 6 patients (18.18%) in Control group. Overall response rate (OR = CR + PR) was 91.43% in the Study group and 84.85% in the Control group.

The 71.4% complete response achieved in our study is comparable to those achieved by Rawat Set al3Patients with histologically proven

stage III - IV B head and neck carcinoma presenting from June 2013 to March 2014 were randomly assigned to weekly (35 mg/m2, 6 cycles; arm A) and 3 weekly (100 mg/m2, 3 cycles; arm B) cisplatin with concurrent radiotherapy.60 patients were randomly assigned to treatment, 30 in each arm. Median follow-up was 8 months (range 4-13). Response at 3 months was similar for all the patients {Complete Response (66.7% vs 62.1%), p = 0.200}.

Sahoo T K et al4 studied weekly vs three weekly cisplatin in head and neck cancer.With a median follow-up of seven months, in arm A complete response was 73.33% (11/15) and partial response was 26.67%; whereas in arm B complete response was 85.71% (12/14) and partial response was 14.29%, which was not statistically significant. However, there was a trend towards better efficacy in arm B.The overall response rates achieved in our study was also comparable to those of Sahoo T K et al and Kose F et al4,5

CONCLUSION

20 mg/m2 of cisplatin for 5 days every four weeks is a well-tolerated schedule with concurrent radiotherapy with similar efficacy as that of three weekly Cisplatin schedule. So we conclude that 20 mg/m2 of cisplatin for 5 days every four weeks can be safely used with concurrent radiation in locally advanced HNSCC without compromising efficacy.

Large sample size and longer duration of follow up may be needed for strong evaluation of efficacy on LRC, DFS & OS.

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