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To assess and compare the toxicities according to RTOG acute toxicity criteria in cisplatin 20 mg/m^2 5 days every four weekly versus standard 100 mg/m^2 three weekly in locally advanced head and neck cancer (LAHNC) patients.

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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/m^2 5 days every four weekly versus standard 100 mg/m^2 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.

Results: 17.14% patients in study group and 60% in control group had grade ≥2 nausea and vomiting. The result was statistically significant (p = 0.001). 20% patients in study group and 48% patients in control group had grade ≥2 dysphagia.

Conclusion: Acute toxicities like dermatitis, dysphagia and mucositis were seen in both groups but less in study group, statistically not significant and were manageable with simple supportive measures. 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, with less toxicity and without compromising efficacy.

Keywords: Cisplastin, Head neck tumor, Side effect.

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.

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/m^2 on five days group and 3-weekly cisplatin 100mg/m^2 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/m^2 on five days every four weeks with conventional radiotherapy.
- Control arm: Patients were given cisplatin 100 mg/m^2 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/m^2 on five days every four weeks and minimum 3cycles of cisplatin 100

mg/m^2 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 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 2: Dermatitis

	0	%	1	%	2	%	3	%	4	%	p-value
Study Arm (N=35)	2	5.71	8	22.86	19	54.29	6	17.14	0	0	
Control Arm (N=33)	1	3.03	5	15.15	17	51.52	9	27.27	1	3.03	Chi-square = 2.680; P = 0.613 (NS)

The incidence of grade ≥2 dermatitis was more with control group(81.8% vs 71.4%) .

Table : 3. NAUSEA & VOMITING

	0	%	1	%	2	%	3	%	4	%	p-value
Study Arm(N=35)	18	51.43	11	31.43	4	11.43	2	5.71	0	0	Chi-square =18.3; P < 0.001 (S)
Control Arm(N=33)	3	9.09	10	30.3	12	36.36	8	24	0	0	

17.14% patients in study group and 60% in control group had grade ≥2 nausea and vomiting. The result was statistically significant (p = 0.001).

Table 4: Dysphagia

Grade	Study Arm		Control Arm		p-value
	No.	%	No.	%	
0	10	28.57	2	6.06	Chi-square = 9.638; P = 0.075(NS)
1	18	51.42	15	45.45	
2	5	14.28	12	36.36	
3	2	5.71	3	9.09	
4	0	0	1	3.03	

20% patients in study group and 48% patients in control group had grade ≥2 dysphagia.

Table 5: Hematological Toxicity (Anaemia)

Hb	Study Arm		Control Arm		
	No.	%	No.	%	p-value
0	21	60%	8	24.24%	Chi-square = 11.38 p <0.001 (S)
1	10	28.57	11	33.33	
2	2	5.71	7	21.21	
3	2	5.71	7	21.21	
4	0	0	0	0	

11.4% patients in study group and 42.4% patients in the Control group developed grade2 and grade 3 anaemia (p <0.001).

Table 6: Hematological Toxicity (Neutropenia)

TLC	Study Arm		Control Arm		p-value
	No.	%	No.	%	
0	22	62.85%	7	21.21	Chi-square =14.83 P<0.001(NS)
1	10	28.57%	13	39.39	
2	2	5.71%	5	15.15	
3	1	2.86%	8	24.24	
4	0	0	0	0	

8.6% patient in the Study group and 39.4% patients in control group developed grade 2 and above Neutropenia.

DISCUSSION

In our study the 11.4% patients in study group and 42.4% patients in the Control group developed grade 2 and grade 3anaemia. 8.6% patient in the Study group and 39.4% patients in control group developed grade 2 and above Neutropenia. A few patients developed systemic side effects as fever and pneumonia/sepsis, those were managed medically.(p <0.001).

2.87% patients and 9% patients were found to have Grade 2 nephrotoxicity in the Study and Control group respectively. There were significant differences

between study groups according to the nephrotoxicity (p =0.002).

17.14% patients in study group and 60% in control group had Grade ≥2 nausea and vomiting. The result was statistically significant (p = 0.001).

A study by Rades D *et al*[4] compared four different cisplatin-based chemoradiation regimens for LASCCHN including 100 mg/m^2 cisplatin every three weeks (N = 74), 20 mg/m^2 of cisplatin given on five days every four weeks (N = 86), and two cisplatin/5-fluorouracil regimens (N = 49 and N = 102, respectively). Grade III nausea/vomiting (p = 0.003), grade III nephrotoxicity (p = 0.019) and grade III hematotoxicity (p = 0.027) were more common in the 100 mg/m^2 cisplatin group than in the other three groups. Thus, taking into account the results from the available studies comparing 100 mg/m^2 of cisplatin every three weeks to regimens including lower doses of cisplatin with respect to treatment outcomes, similar outcomes can be achieved with lower-dose cisplatin regimens.[5-7] In a meta-analysis by de Castro G *et al*,100 mg/m^2 of cisplatin given concurrently with EBRT every three weeks is considered to be the standard approach, a considerable number of centers are hesitant to use this regimen because of its high toxicity.[8]

Conclusion

Acute toxicities like dermatitis, dysphagia and mucositis were seen in both groups but less in study group, statistically not significant and were manageable with simple supportive measures. 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, with less toxicity and without compromising efficacy.

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