A PROSPECTIVE RANDOMIZED STUDY COMPARING CARBOPLATIN AND CAPECITABINE BASED CHEMORADIATION VERSUS CARBOPLATIN AND 5FU BASED CHEMORADIATION IN LOCALLY ADVANCED HEAD AND NECK CANCER

Shalini Verma¹, Manoj Gupta², Srinivas Gowda³, Jyoti Singh⁴, Sumit Kumar⁵, Vishal Kaundal⁶, Rajeev Seam⁷, Manish Gupta⁸

^{1,3-5} Senior Resident, ^{2,7,8} Professor, ⁶ Medical Officer

^{1,2,3,8} Indira Gandhi Medical College, Regional Cancer Centre Shimla

^{4,5} AIIMS Delhi

⁷ Dr Rajendra Parsad Government Medical College, Kangra at Tanda, Himachal Pradesh

Article Info: Received 28 June 2019; Accepted 30 July. 2019

DOI: <https://doi.org/10.32553/ijmbs.v3i8.444>

Address for Correspondence: Shalini Verma, Om niwas keshar Bagh colony near chaudhary clinic , palampur distt kangra, 176061

Conflict of interest: No conflict of interest.

Abstract

Background: In this study we took care of convenience for the patient and hospital staff while limiting hospital burden at the same time and compare its toxicities and disease response with concurrent Carboplatin with 5FU based CRT.

Methods: This prospective randomized study was conducted in the Department of Radiotherapy & Oncology, Regional Cancer Centre , IGMC, Shimla. It included all the previously untreated adult patients of squamous cell carcinoma of Head and Neck with histologically confirmed diagnosis and no evidence of distant metastasis.

Results: Treatment was interrupted in 16.2% of patients in the Carboplatin with Capecitabine arm and 8.1% patients in the Carboplatin with 5FU arm.

Conclusion: Higher toxicities were seen in carboplatin with Capecitabine arm as compared Carboplatin with 5FU arm though not statistically significant. This again require further validation on large sample size.

Keywords: Carboplatin, Capecitabine, 5FU, Cancer.

Introduction:

The term “head and neck cancer” usually refers to neoplasms arising from below the skull base to the region of the thoracic inlet. The majority of the head and neck malignancies arise from the different anatomic subsites and air spaces bounded within these regions. The head and neck cancer is commonly a squamous cell carcinoma and other histologic entities are uncommon.

Head and neck malignancies constitute 5% of all the cancers worldwide. In India according to National Cancer Registry Programme (ICMR), squamous cell carcinoma of head and neck region accounts for 29.6% of all cancers in male (range 24.3% - 34.3%) and 11.84% of all cancers in females (range 10.5 % - 15.5%) in different hospital registries in India¹.

Approximately 40,000 patients are newly diagnosed annually with squamous cell carcinoma of head and neck in United States. Worldwide approximately

600000 patients are afflicted. This represents 2.9% of the total new cancer cases². Nearly 60% of this population present with locally advanced, but non-metastatic disease. Locoregional failure constitutes the predominant recurrence pattern with most fatality results from uncontrolled local and / or regional disease².

In Regional Cancer Centre, Indira Gandhi Medical College, Shimla Head and Neck cancers represent 16% of all cancers registered from 2001 to 2010. Over this period these represented 10.6% of all cancers in males and 5.4% of all females cancers. The geographic distribution reveals very large variation in different countries and regions with low incidence reported in Western Europe and high incidence in South Asia, parts of Africa and South America.

In this study we took care of convenience for the patient and hospital staff while limiting hospital burden at the same time and compare its toxicities

and disease response with concurrent Carboplatin with 5FU based CRT.

Thus this trial has made a comparison to achieve same or near to the same local control and tolerability to that of carboplatin and 5FU within the affordable range of Indian population and to see whether capecitabine can replace 5FU in head and neck cancer this approach needs further attention or not.

MATERIAL AND METHODS

This prospective randomized study was conducted in the Department of Radiotherapy & Oncology, Regional Cancer Centre, IGMCI, Shimla. It included all the previously untreated adult patients of squamous cell carcinoma of Head and Neck with histologically confirmed diagnosis and no evidence of distant metastasis. The subsites included will be oro-pharynx, hypo-pharynx and larynx with stages III, IV A and IV B for a period of one year (from July, 2013 to July, 2014)

It was a prospective randomized two arm study in histologically confirmed cases. All patients will be of the age not more than 70 years and having Karnofsky performance status score more than 70 with normal renal function tests and liver function tests and hemoglobin level more than 10 gm%.

Inclusion Criteria:-

- Age $\leq$ 70yrs.
- Sites – oropharynx, hypopharynx, larynx.
- Histology – squamous cell carcinoma.
- Stage III, IV A and IV B.
- Previously untreated patients.
- Hb $>$ 10gm%.
- Pretreated leucocyte count of $>$ 4000/cu mm.
- Platelet count $>$ 100,000/cu mm.
- Normal renal and liver function tests.
- Karnofsky performance status $>$ 70.

Exclusion Criteria:-

- Histology other than squamous cell carcinoma.
- Sites other than oropharynx, hypopharynx, and larynx.
- Age $>$ 70yrs.
- Deranged RFT / LFT.

- Karnofsky performance status $<$ 70.
- Distant metastasis.

Randomization:-

Randomization was carried out by stratification, the treatment assignment was stratified according to site of disease (hypopharynx, larynx, oropharynx), N stage (node –ve or +ve) and T stage (T1, T2 vs T3, T4) of disease. Patients were randomized into two groups: one study and control group based on treatment they received. Approximately equal numbers were assigned to each group.

Study Design:-

Control arm: Patients were subjected to standard concurrent chemoradiotherapy. Patients were given radiation one fraction per day (TOTAL: 66Gy/6½wks/33#), on five consecutive days from Monday to Friday along with intravenous carboplatin 70 mg/m² (max. 100mg) day 1 to 4 by continuous i/v infusion repeated every 21 days for 2 cycles.

Study arm: Patients were subjected to concurrent chemoradiotherapy. Patients were given radiation one fraction per day (Total: 66Gy/6½wks/33#), on five consecutive days from Monday to Friday along with intravenous carboplatin 70 mg/m² D1-4 of each cycle with Capecitabine 500mg 2 b.i.d on days 1-14 was repeated on day 22 for total of 2 cycles.

Administration Of Treatment :-

External beam radiation therapy was given by Theratron® 780e or Equinox™ Cobalt-60 machines using either two parallel and opposed fields or three field technique. Orfit cast was used for immobilization in all the patients. Initially the radiation portals encompassed primary disease, involved lymph nodes and microscopic disease around primary & in clinically uninvolved lymph nodes. In most of the cases whole neck along with primary disease was included in the initial radiation portals. After 44Gy/22#, the posterior neck field was reduced to spare spinal cord. After the microscopic disease had received 50Gy/25#, the field was reduced to include involved lymph node region with one level up. After 60Gy/30# the field was reduced to include involved primary sites with primary echelon and involved lymph nodes.

Chemotherapy

Carboplatin was administered with a dose of 70 mg/m² of body surface area In 500 ml D5.

Antiemetics in the form of 5-hydroxytryptamine inhibitors antagonists (ondansetron 8mg) was co-administered before and after chemotherapy. Weekly complete haemograms, renal & liver function tests were done. Cap capecitabine was given from Day 1-4 at a dose of 500 mg2 BID.

Inj 5FU was given in a dose 400 mg/m² D1-4 as continuous infusion in NS.

Statistical analysis:-

Response rate was the primary end point for analysis. The various prognostic factors effecting response were also be analysed. The data obtained from both arms were analysed by student "t"-test and chi-square test.

OBSERVATION

Age of the patients ranged between 37 to 70 years with median age of presentation being 56.2 years and mean age 56 years. Most of the patients were in the 51-60 yrs age group. Both the arms were balanced with regards to age distribution. Out of 74 patients, 66 patients (89.1%) were males and 8 patients (10.8%) were females. In the Carboplatin with capecitabine arm, out of 37 patients, 32 patients

(86.5%) were males and 5 patients (13.5%) were females. In the Concurrent carboplatin with 5FU arm, out of 37 patients, 34 patients (91.9%) were males, and 3 patients (8.1%) were females. Both the arms were well matched with respect to sex distribution.

Out of total 74 patients, 69 patients (93.2%) were smokers where as 5 patients (6.8%) were non-smokers. In the Concurrent carboplatin with capecitabine arm, out of 37 patients, 33 patients (89.2%) were smokers and 4 patients (10.8%) were non-smokers. In the Concurrent Carboplatin with 5FU arm, out of 37 patients, 36 patients (97.3%) were smokers and 1 patients (2.7%) was non-smoker. Both the groups were matched.

Out of 74 patients, 17 patients (23%) were CA (chronic alcoholics), 39 patients (52.7%) were OA (occasional alcoholics) and 18 patients (24.3%) were NA(non-alcoholics). In the Concurrent Carboplatin with capecitabine arm, out of 37 patients, 7 patients (18.9%) were chronic alcoholics, 21 patients (56.8%) were occasional drinkers and 9 patients (24.3%) were non-alcoholics. In the Concurrent Carboplatin with 5FU arm, out of 37 patients, 10 patients (27%) were chronic alcoholics, 18 patients (48.6%) were occasional alcoholics and 9 patients (24.3%) were non-alcoholics. Both the arms were matched.

Table 1: Skin toxicities observed during radiotherapy

Skin toxicities	Treatment group		Total	P value
	Arm 1	Arm 2		
	(n=37)	(n=37)		
G1	3 (8.1%)	4 (10.8%)	7 (9.4%)	0.71
G2	10 (27.0%)	11 (29.7%)	21 (28.4%)	0.797
G3	20 (54.0%)	20 (54.0%)	40 (54.0%)	
G4	4 (10.8%)	2 (5.4%)	6 (7.7%)	0.44

Skin toxicities ranging from G1 to G4 were seen in both the arms during treatment. Most of the patients suffered from G3 toxicity which was equal (54%) in both the arms. Grade 4 toxicity was slightly higher in Concurrent Carboplatin with capecitabine arm but difference was not statistically significant (10.8%Vs 5.4%, p=0.44)

Table 2: Mucositis during radiotherapy

Mucositis	Treatment Group		Total	p value
	Carbo+Capec (n=37)	Carbo+5FU (n=37)		
G0	0 (0%)	0 (0%)	0 (0%)	
G1	2 (5.4%)	4 (10.8%)	6 (8.1%)	0.437
G2	12 (32.4%)	18 (48.6%)	30 (40.5%)	0.156
G3	20 (54.0%)	12 (32.4%)	32 (43.2%)	0.06
G4	3 (8.1%)	3 (8.1%)	6 (8.1%)	1
Total	37 (100%)	37 (100%)	74 (100%)	

Mucositis was seen in both the arms during treatment. Majority of patients developed grade 3 i.e. confluent mucositis with severe pain requiring narcotic analgesia. In Carboplatin with capecitabine arm 32.4% patients and in Carboplatin with 5FU arm 48.6% patients developed grade 2 mucositis. However Grade 3 toxicity was higher in the Carboplatin with capecitabine group as compared to Carboplatin with 5FU group but difference was not statistically significant. (54% vs. 32.4%, $p=0.06$).

Table 3: Laryngeal toxicity during radiotherapy

Laryngeal Toxicity	Treatment Group		Total	p value
	Carbo+Capec (n=37)	Carbo+5FU (n=37)		
G0	6 (16.2%)	11 (29.7%)	17 (23%)	0.167
G1	24 (64.9%)	24 (64.9%)	48 (65%)	
G2	6 (16.2%)	2 (5.4%)	8 (10.8%)	0.158
G3	0 (0%)	0 (0%)	0 (0%)	
G4	1 (2.7%)	0 (0%)	1 (2.7%)	0.314
Total	37 (100%)	37 (100%)	74 (100%)	

Laryngeal toxicities ranging from G0 to G4 were seen in patients during treatment in both the arms. G1 laryngeal toxicities were seen in majority of patients followed by persistent hoarseness or whispered speech, throat pain requiring narcotics and cough requiring antitussives (i.e G2 , laryngeal toxicities) Grade 4 laryngeal toxicity was seen only in 1 patient in carboplatin with capecitabine arm. But all these toxicities were transient and were managed conservatively. The frequency of patients who experienced Grade2 laryngeal toxicity in Carboplatin with Capecitabine arm as compared to Carboplatin with 5FU arm was higher but difference was not statistically significant. (16.2% vs 5.4%, $p=0.158$) combined together Grade 1 and Grade 2 toxicities were higher in Carboplatin and Capecitabine arm as compared to Carboplatin and 5FU arm but the difference was not statistically significant.(81.1% vs 70.3%, $p=0.28$)

Table 4: Pharyngeal toxicity during radiotherapy

Pharyngeal Toxicity	Treatment Group		Total	p value
	Carbo+Capec (n=37)	Carbo+5FU (n=37)		
G0	5 (13.5%)	1 (2.7%)	6 (8.1%)	0.11
G1	21 (56.8%)	28 (75.7%)	49 (66.2%)	0.085
G2	9 (24.3%)	8 (21.6%)	17 (23%)	0.78
G3	2 (5.4%)	0 (0%)	2 (2.7%)	0.151
G4	0 (0%)	0 (0%)	0 (0%)	
Total	37 (100%)	37 (100%)	74 (100%)	

The low grade pharyngeal toxicity (i.e G1 and G2) was more commonly seen in patients of both arms. The G1 pharyngeal toxicities were higher in the Carboplatin with 5FU arm (75.7%) as compared to the Carboplatin with Capecitabine arm (56.8%) whereas G2, G3 pharyngeal toxicities were higher in Carboplatin with Capecitabine arm (29.7%) as compared to Carboplatin with 5FU arm (21.6%) but the difference was not statistically significant ($p=0.42$).

All these toxicities were transient and were managed conservatively.

Table 5: Salivary gland toxicity

Salivary Gland Toxicity	Treatment Group		Total	p value
	Carbo+Capec	Carbo+5FU		
G0	0 (0%)	1 (2.7%)	1 (1.4%)	
G1	32 (86.5%)	32 (86.5%)	64 (86.5%)	0.74
G2	5 (13.5%)	4 (10.8%)	9 (12.1%)	
Total	37 (100%)	37 (100%)	74 (100%)	

Salivary gland toxicities ranging from grade 0 to grade 2 were seen in both the arms. Moderate to complete dryness of mouth, thick sticky saliva, marked altered taste (i.e. G2 toxicity) were seen slightly higher in Carboplatin with Capecitabine arm (13.5%) as compared to Carboplatin with 5FU arm (10.8%). G1 toxicity was equal in both arms (86.5%).

Table 6: Haematological Toxicity

Haematological Toxicity	Treatment Group		Total	p value
	Carbo+Capec (n=37)	Carbo+5FU (n=37)		
G0	18 (48.6%)	19 (51.4%)	37 (50%)	0.82
G1	13 (35.1%)	13 (35.1%)	26 (35.1%)	
G2	4 (10.8%)	5 (13.5%)	9 (12.2%)	0.74
G3	2 (5.4%)	0 (0%)	2 (2.7%)	0.314
Total	37 (100%)	37 (100%)	74 (100%)	

The G1 haematological toxicities were same in the Carboplatin with 5FU and Carboplatin with capecitabine arm. 13 patients (35.1%) had G1 toxicity in both arms and 4 patients (10.8%) had G2 haematological toxicity and 5 (13.5%) Carboplatin and Capecitabine arm and Carboplatin with 5FU arms respectively. G3 toxicity was seen only in Carboplatin with Capecitabine (5.4 % vs 0%)

Table 7: Treatment Interruption

Treatment Interruption	Treatment Group		Total	p value
	Carbo+Capec	Carbo+5FU		
	(n=37)	(n=37)		
Yes	6 (16.2%)	3 (8.1%)	9 (12.1%)	0.316
No	31 (83.8%)	34 (91.9%)	65 (87.8%)	
Total	37 (100%)	37 (100%)	74 (100%)	

Treatment was interrupted in 16.2% of patients in the Carboplatin with Capecitabine arm and 8.1% patients in the Carboplatin with 5FU arm.

The reason for treatment interruption in carboplatin with Capecitabine arm was G3 and G4 skin toxicity in 1 patient, G3, G4 mucositis in 1 patient, poor G.C in this arm and One patient had G4 Laryngeal toxicities in Carboplatin with Capecitabine arm and one patient had haematological toxicity (low platelet and low TLC with poor general condition) and one patient had herpes zoster in the same arm.

One patient in Carboplatin and 5FU arm had treatment interruption due to non compliance of patient that time, One patient in Carboplatin with 5FU arm, one patient in this arm had poor general condition, one patient in this arm had skin and mucosal reaction.

DISCUSSION

This study was planned with the objectives that: -

1. Reducing the need of continuous i.v infusion by replacing Inj 5FU with Cap Capecitabine and thereby eliminating hospital stay for long days and bringing same or near to same loco regional control as with concurrent Carboplatin with 5FU.
2. And making it convenient to the patient and staff and to compare the tolerability of Concurrent CRT with Cap Capecitabine with Carboplatin over CRT with Carboplatin with 5FU.

During last one year i.e. from 1.7.2013 to 31.07.2014 we accrued 74 patients in two arms, 37 in Concurrent CRT- Carboplatin with Capecitabine arm and 37 in concurrent CRT-Carboplatin with 5FU arm. All these

patients are well balanced with regard to all clinical parameters like age and sex distribution, smoking, alcohol consumption and dietary habits distribution, T-stage and nodal stage distribution and site wise distribution of disease. Median overall time for completion of treatment was 45 days in both the arms. Among the patients in the Carboplatin with Capecitabine arm 16.2% (6 patient) had treatment interruption whereas in the Carboplatin with 5FU arm 8.1% (3 patients) had treatment interruption. Though the difference was not significant statistically but there seems to be a trend of more interruption in study arm.

We observed that during radiation treatment Confluent fibrinous mucositis with pain (Grade 3 acute mucositis) was seen more in the carboplatin with Capecitabine arm (54%) as compared to Carboplatin with 5FU RT arm (32.4%). This severe mucositis was managed conservatively with frequent oral rinses and gargles, local anaesthetics, antifungals and analgesics. Again the difference was not significant statistically but more severe toxicity observed in study arm.

In the study by Dogbin Ahn et al³, 31 patients with stage III/ IV resectable LHSCC treated with concurrent chemoradiotherapy using cisplatin (60 mg/m²) and Capecitabine (825mg/m²) bid for 14 days with 66-72 Gy RT, G3 mucositis was found in 25.6% which is much lesser than observed in our capecitabine arm. This difference can be due to lesser dose of cisplatin used in their study.

Grade 3 skin toxicities were seen in 54% of the patients in both arms. Grade 4 skin toxicities were higher in the carboplatin with Capecitabine arm

(10.8%) as compared Carboplatin with 5FU arm (5.4%). Again these were managed with topical applications of epidermal growth factor ointment, oral antibiotics and systemic antibiotics if needed. Here also a trend of higher toxicity was observed in study arm though the difference in skin toxicity was not statistically significant.

Likewise persistent hoarseness or whispered speech with throat pain and cough (G2, laryngeal toxicity) was seen in higher number of patients in the concurrent Carboplatin with Capecitabine arm. In the Carboplatin with Capecitabine arm 16.2% patients and in carboplatin with 5FU arm 5.4% patients experienced G2 acute laryngeal toxicity. This was also managed conservatively with non narcotics and narcotic analgesics, antitussives, steroids and antibiotics. Grade 4 toxicity was seen only in Carboplatin with Capecitabine arm (2.7%). This difference in toxicity was not statistically significant.

Moderate to severe dysphagia or odynophagia requiring semisolid or liquid diet and narcotic analgesics with intravenous fluids and nutritional supplementation (G2-G3 pharyngeal toxicity) was seen in more number of patients in the Capecitabine arm (29.7% vs 21.6% ; $p=0.34$).

In our study Hand foot syndrome was found in 8.1% in Carboplatin with Capecitabine arm and 2.7% in Carboplatin with 5FU arm.

In our study a trend of higher acute toxicities were observed in Capecitabine arm as compared to 5FU arm . However this difference in acute toxicities was not significant statistically . The statistical significance may not be reached due to small sample size . This observation needs to be evaluated further on large randomized trials.

Grade 2 haematological toxicity was slightly higher in 5FU arm (13.5% vs 10.8%) but Grade 3 toxicity was only seen in Capecitabine arm (5.4% vs 0%).

A study by Maroie Barkati et al⁶⁹ found that in carboplatin and 5FU arm (70mg/m² and 600 mg/m² for 4 days, 3 cycles with 70Gy, G3-G4 haematological toxicity was 10.1%. In the study by Dogbin Ahn et al³, 31 patients with stage III/ IV resectable LAHSCC treated with concurrent chemoradiotherapy using cisplatin (60 mg/m²) and Capecitabine (825mg/m²) bid for 14 days with 66-72 Gy RT, G3,G4 haematological toxicities were found in 12.9%. Our results were comparable to earlier studies in relation to haematological toxicity.

CONCLUSION

Higher toxicities were seen in carboplatin with Capecitabine arm as compared Carboplatin with 5FU arm though not statistically significant. This again require further validation on large sample size.

REFERENCES

1. National Cancer Registry Programmed: Ten year consolidated report of the hospital based cancer registries 1984-1993.ICMR, New Delhi.
2. Brizel DM. The role of combined radiotherapy and chemotherapy in the management of locally advanced squamous carcinoma of the head and neck. In: Halperin EC, Perez CA, Brady LW, eds. Principles and Practice of Radiation Oncology, 5th edn, Lippincott Williams & Wilkins, Philadelphia 2008.807-19.
3. Dogbin Ahn, Jae Hyug Kim, Jin H Sohn, Chang-Min Sin, Jeong Eun Lee. Laryngeal preservation in stage III/IV resectable laryngo-hypopharyngeal squamous cell carcinoma following concurrent chemoradiotherapy with capecitabine/cisplatin. Molecular And Clinical Oncology.2013; 1: 685-691.