A study on treatment of locally advanced squamous cell carcinoma of head and neck with radiation along with cisplatin or gefitinib

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Abstract

Background: Cisplatin based Concurrent chemo-radiation (CTRT) is the corner stone for treatment of locally advanced head and neck carcinoma. Epidermal growth factor receptor(EGFR) expression by squamous cell carcinoma which is associated with cancer development and progression,leads to emergence of anti-EGFR agents as a therapeutic option. In this study we compare cisplatin based CTRT against gefitinib based CTRT in terms of disease control and acute toxicity profile.

Material and Methods: Stage III and IV squamous cell carcinoma of Head and neck region (excluding nasopharynx) were randomised into two groups. Control group received conventionally fractionated radiotherapy of 66Gy in 33fractions, over six and half weeks with concurrent weekly cisplatin. Study group received same dose of radiation with concurrent daily oral Gefitinib. All patients were followed up weekly during the treatment and then 6-8 weeks after completion of treatment and thereafter 3 monthly.

Results: Overall response rate (complete response + partial response) was comparable for both arms (75% vs 76.2%, p value-0.881). Radiation with cisplatin was associated with significantly higher skin (28.6% vs 15%,p value-0.037) and mucosal (23.8% vs 5%,p-value-0.047) toxicities. Gefitinib containing arm showed significantly higher grade 3 diarrhoea (10% vs 0%, p-value-0.01) and skin rash (6% vs 0%, p -value-<0.001).With a median follow-up of 12.5 months Disease free survival (DFS) was not significantly different between the arms(12 vs 13 months).

Conclusion: Gefitinib based CTRT is non-inferior to cisplatin based CTRT for the treatment of locally advanced head and neck carcinoma with acceptable toxicity profile.

Key words: Locally advanced Head and Neck carcinoma, concurrent chemo-radiation, Cisplatin, Gefitinib.

Introduction

Every year nearly 6.5 lakhs people develop Head and Neck Cancer World-wide. In India cancers of lip and oral cavity constitute the second most common cancer (10.3%) according to GLOBOCAN 2020 data[1,2].

The treatment options for patients presenting with locally advanced head and neck cancers include definitive concurrent chemo-radiation or induction chemotherapy followed by chemoradiation or radiation with surgery reserved as a possible salvage option for residual and recurrent disease depending upon the sub-site of primary. Concurrent chemo-radiation (CTRT) has emerged as an acceptable definitive treatment for locally advanced carcinoma of head and neck region[3]. Robust and mature data from various randomised studies and meta-analysis MACH-NC have favoured platinum based chemo-radiation[4].

Study of tumour biology revealed epidermal growth factor receptor (EGFR) as a predictor of radiation response of Head and Neck carcinoma and have identified EGFR and it's downstream signaling molecules as appealing targets for therapeutic intervention[5-8].The results of a recently completed international trial in 2014showed that adding an anti-EGFR antibody to radiation yielded improved

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locoregional tumour control and overall survival without increasing mucositis and dysphagia as compared with radiation alone[9].Apart from monoclonal antibodies, EGFR tyrosine kinase inhibitors like Gefitinib has emerged as an effective therapeutic option for squamous cell carcinoma of head and neck region[10].Phase II Study by Doss et al that used induction chemotherapy followed by CTRT/ radiation/Gefitinib for locally advanced head and neck carcinoma had an overall response rate of 85% with improved overall survival at 1 year[11].But, there is lack of adequate evidence comparing cisplatin and gefitinib as concurrent agent with radiation therapy.

With this background, in this study we compared radiation therapy with concurrent gefitinib against cisplatin based concurrent chemo-radiation therapy in terms of disease control,disease free survival and acute treatment related toxicities.

Material and Methods

It was a double arm**,** single institutional, prospective, comparative study in patients of stage III or IV (any T,N1-3M0;T3-4N0M0) squamous cell carcinoma of Head and neck region aged between 18-70 years having adequate hepatic, renal, hematological parameters and an ECOG score of 0-2. Patients with nasopharyngeal carcinoma, histology other than squamous cell carcinoma, recurrent carcinoma, previous history of any other malignancy or chemotherapy or radiotherapy were excluded. The study was conducted between January 2019 and April 2020.

Study technique:

Patients were selected using above mentioned inclusion and exclusion criterias and randomized into two groups-

Control arm: patients in this group received Conventionally fractionated radiotherapy toa total dose of 66Gy in 33fractions over a time period of six and half weeks with concurrent weekly intra-venous Cisplatin at a dose of 40mg/m^2.

Study arm: patients of this group received radiotherapy with same dose like control arm with concurrent Tablet Gefitinib 250 mg daily orally. Patients were instructed to start tablet Gefitinib from the morning of starting radiotherapy in empty stomach and to continue till the end of radiation treatment.

Radiotherapy technique:

Radiotherapy was delivered by means of conventional 2D planning based on anatomic bony landmarks using "Theratron 780E" telecobalt machine.

Patient position:

Supine with neck extended, immobilized with the help of head rest (Type A,B,C).

Radiation portals:

Treatment portals were selected depending on the tumour extension and nodal status. Bilateral parallel opposed fields with or without Low Anterior neck field were used for all patients. Dose prescription was done at centre of inter field distance (IFD) in lateral parallel opposed field and at depth of three cm in case of direct anterior field used for lower neck treatment.

For lesions involving skin or tracheostomy stoma, bolus were used to increase the superficial skin dose.

Conventional Two-phase planning was used to deliver the radiation dose-

PHASE I- Total 44 Gy in 22 fractions.

Two lateral parallel opposed facio-cervical field including the primary and draining lymph node groups were used to deliver EBRT in Phase I.A matched anterior neck field to treat the lower neck nodes with midline shielding to reduce dose to the larynx, pharynx and spinal cord was used for some patients.

PHASE II- Dose of 22 Gy in 11 fractions over 2 weeks in conventional fractionation given.

Two parallel opposed facio-cervical fields were used here also. But, here the posterior border of the lateral facio-cervical fields were shifted from tip of mastoid process to tragus to spare the spinal cord (OFF CORD) depending on clinical situation.

The conventional field borders were followed based on the standard surface markings and by landmarks as described in Fletcher's text book of radiotherapy[12].

Follow-up

All patients were followed up weekly for treatment related acute toxicity during the entire course of treatment. Then 6-8 weeks after the completion of treatment patients were first followed up with proper history, detailed ENT (Ear-nose-throat) &clinical examination, CBC, LFT, KFT parameters and other necessary investigations as indicated including imaging. Thereafter patients were followed up at 3 monthly intervals till the end of the study or till appearance of recurrent disease.

Response assessment was done using RECIST1.1 after completion of treatment. Treatment related toxicities were assessed as per toxicity assessment tools-CTCAE (Common terminology criteria for adverse events scale v5.0) and with Radiation therapy oncology group (RTOG) scoring. Patients developing grade III or above toxicity were given treatment interruption and were managed as required.

Patients with progressive/recurrent disease were managed with chemotherapy or surgery as per requirement.

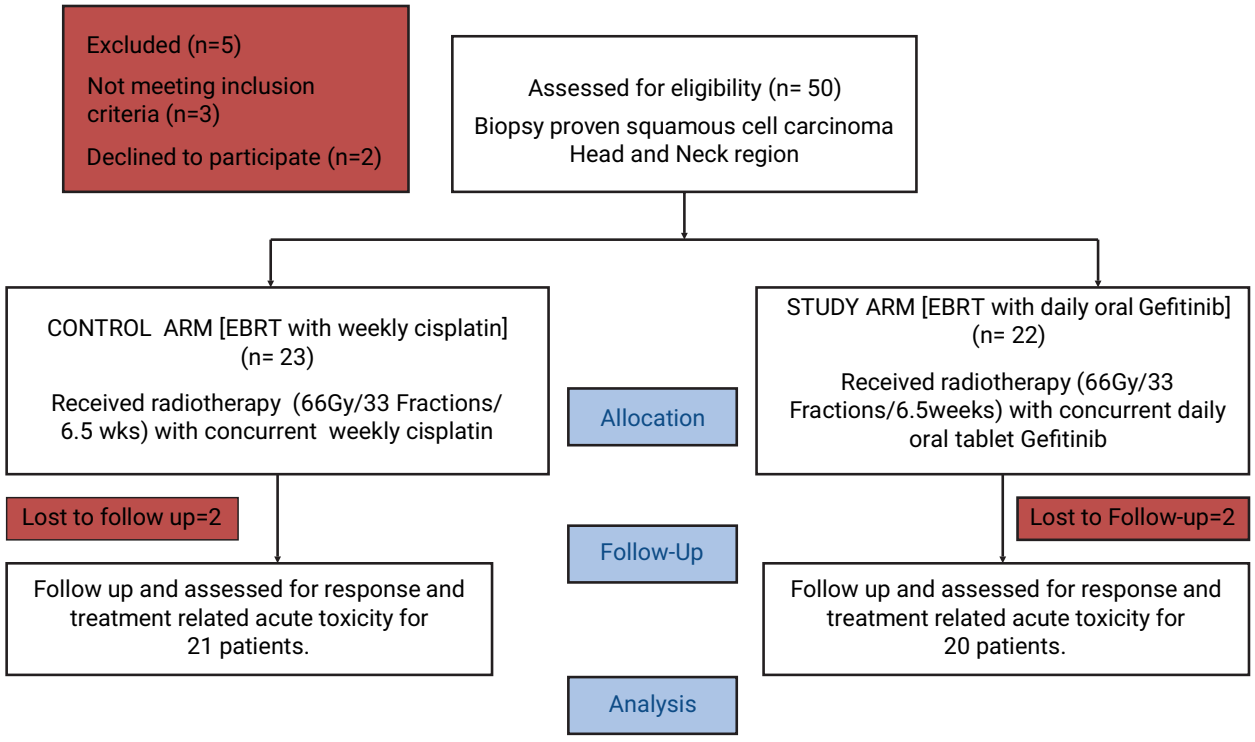
Approval for study was taken from institutional ethics committee.

Statistical analysis:

Data was analyzed and compared according to appropriate statistical tests using SPSS v.20 software and Microsoft word-excel. For categorical variables, Chi-Square and Fisher Exact tests were used, while for continuous variables, the mean and SD were compared using independent samples t test with 95% confidence interval (CI).All tests were 2-tailed and p value less than 0.05 was taken as significant. The disease free survival (DFS) was determined using the Kaplan Meier survival analysis with Log Rank test for comparing the DFS.

Results

Consort diagram



Baseline characters

Both the arms of the study were comparable in terms of mean age of the patients, gender, primary site of disease, stage of disease at presentation, performance status at the initiation of study and EGFR expression status.

Table1: Comparison of Baseline Characteristics Between Two Arms of Study

Characteristics		Arm of the Study		P Value
		Study Arm (N=20)	Controlarm (N=21)	
Mean Age of Patients (In Years)		58.15	56.38	0.440
Gender	Male	18	18	0.675
	Female	02	03	
	Total	20	21	
Primary Site Of Disease	Oropharynx	09	10	0.986
	Hypopharynx	06	05	
	Larynx	05	06	
	Total	20	21	
Stage of Disease At Presentation	III	13	12	0.912
	Iva	07	09	
	Total	20	21	

Performance Status (ECOG Score)	1	14	15	0.530
	2	06	06	
	Total	20	21	
EGFR Expression Status	Positive	09	07	0.444
	Negative	11	14	
	Total	20	21	

Assessment of tumor response

Overall treatment response (complete response + partial response) was statistically comparable among both the arms (75% vs 76.2%, p-value-0.881).

Table 2: Comparison of Treatment Response

Arm	Treatment Response				Total	P Value
	Complete Response	Partial Response	Stable Disease	Progressive Disease		
Study	09	06	02	03	20	0.881
Control	11	05	03	02	21	
Total	20	11	05	05	41	

Assessment of treatment related toxicity:

Skin toxicity of Grade 2 and above was significantly higher in cisplatin containing arm (control arm) than gefitinib containing study arm (66.6% vs 25%, p-value-0.037**).**

Table 3: Comparison of Acute Skin Toxicity

Arm	Acute Skin Toxicity				Total	P-Value
	Grade 0	Grade 1	Grade 2	Grade 3		
Study	05	10	02	03	20	0.037
Control	04	03	08	06	21	
Total	09	13	10	09	41	

Incidence of high grade acute mucositis (Grade 2 and above) was also higher in control arm (66.67% vs 25%).In terms of acute mucosal toxicity these differences were statistically significant (p-value- 0.047).

Although Grade 2 xerostomia was numerically higher in study arm (46% vs 29%), but the difference was not statistically significant(p-value-0.155)**.**

Table 4: Comparison of Xerostomia Between Two Arms

Arm of Study	Xerostomia			Total	P-Value
	Grade 0	Grade 1	Grade 2		
Study	08	09	03	20	0.004
Control	03	04	14	21	
Total	11	13	17	41	

Incidences of Grade 2 or above diarrhoea was significantly higher in study arm patients in comparison to control arm (55% vs 9%, p value-0.01)

Table 5: Comparison of Diarrhoea Between Two Arms

Arm	Diarrhoea				Total	P-Value
	Grade 0	Grade 1	Grade 2	Grade 3		
Study	04	05	09	02	20	0.010
Control	13	06	02	00	21	
Total	17	11	11	02	41	

There was no incidence of skin rash among patients received cisplatin (control arm) whereas around 80% patients who received gefitinib had skin rash. This difference was statistically significant (p value <0.001).

Table 6: Comparison of Skin Rash Between Two Arms

Arm	Skin Rash			Total	P-Value
	Grade 0	Grade 1	Grade 2		
Study	04	10	06	20	<0.001
Control	21	00	00	21	
Total	25	10	06	41	

Comparison of disease free survival

With a mean follow-up of 12.5 months, 33.33% patients of study arm had recurrence in comparison of 27.3% in control group. Kaplan Meier analysis showed statistically non-significant disease free survival between the two arms of the study (chi-square 0.237, log rank test 0.626).

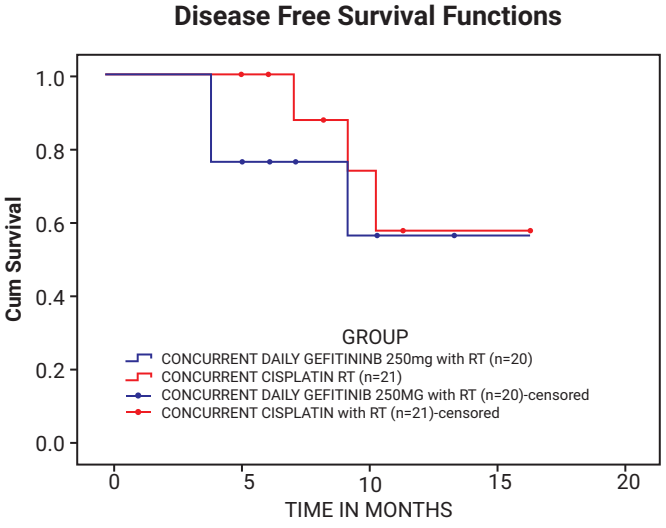


Figure 1: Comparison Of Disease Free Survival Between Two Arms

Discussion

Advantages of concurrent chemo-radiation over radiation alone in the therapy of advanced head and neck carcinoma have been found in both definitive and post-operative setting, using cisplatin as the main chemotherapeutic agent. Better understanding of cancer pathogenesis, pathways involved, growth factors and knowledge of proteins involved in these activities have led to the concept of targeted therapy.

Head and neck carcinoma which is known to express EGFR also has been the focus for targeted therapy. Agents being studied are either monoclonal antibodies (cetuximab) or tyrosine kinase inhibitors (Gefitinib or Erlotinib etc.). Pre-clinical studies suggested the radiosensitizing ability of EGFR Antagonists by a variety of mechanisms including reduction in the proportion of cells in the radioresistant S phase by inducing cell cycle arrest at G0-G1 phase, inhibition of radiation induced DNA damage repair and induction of apoptosis[13]. With this background we did this study to evaluate Gefitinib as an alternative agent to cisplatin for using concurrently with radiation.

Mean age of patients was 58.15 years in study arm (Gefitinib) and 56.38 years in control arm (cisplatin) which was consistent with average age of presentation of head and neck carcinomas. Around 88% of study population was male which is in accordance with the gender based incidence and prevalence of head and neck cancers[14].Baseline characteristics of both the arms were comparable in terms of age of presentation, sex distribution, stage at presentation, performance status at the initiation of study (ECOG score), primary site of disease and EGFR expression status(Table 1).

In our study, there was slightly better complete response rate seen in cisplatin containing control arm than gefitinib containing study arm (52.3% vs 45%). But, overall response (complete + partial response) was almost same in both the arms (76.2% vs 75%). There was no statistically significant difference (p-value-0.881) (Table 2).There is no direct evidence comparing the effectiveness of cisplatin against gefitinib as concurrent therapy. But, study by Saini et al showed that although the combination of Gefitinib and cisplatin concurrently with radiation was well tolerated, but does not significantly effect the response rate, progression free survival and overall survival[15].

Incidences of grade 3 skin reactions (15% vs 28.6%, p-value-0.037) and mucositis (5% vs 23.8%) was significantly higher in cisplatin based CTRT than gefitinib based CTRT (Table 3).

In phase I study by Changhu Chen et al, incidence of grade 3 or higher mucositis was around 62.5% for gefitinib based CTRT[16]. These findings were much higher than our study because in that study they used altered fractionation radiotherapy along with gefitinib whereas we used conventionally fractionated radiotherapy.

Combined incidence of grade 2 or higher gastro-intestinal toxicity (diarrhoea) was 55% for gefitinib containing arm in comparison with 9.5% of cisplatin containing arm. Incidences of higher grade (grade 2 or more) of skin rash was also higher in study arm (80% vs 0%). Both the differences were statistically significant (p-value- 0.010 and <0.010 respectively) (Table 5,6).These higher incidence of skin rash and diarrhoea was due to the gefitinib specific toxicity, it was not associated with radiation. This toxicity profile is consistent with previous studies also[17].

With a mean follow up of 12.5 months there was recurrence in 33.33% patients of gefitinib containing

study arm (mean survival time in months 12± 1.8,95% CI 8.35 to 15.59) compared to 27.3% in cisplatin containing control arm (mean survival 13± 1.3,95% CI 10.47 to 15.67).Kaplan Meier survival analysis showed non-significant difference in disease free survival (DFS) between these two arms (log rank test 0.2) (Figure 1).

Overall our study showed Gefitinib based concurrent chemoradiation was non-inferior to cisplatin based CTRT with no significant difference in disease free survival (DFS) between the two arms after a median follow-up of 12.5 months. Radiation induced skin and mucosal toxicities were significantly less in gefitinib based treatment than that of cisplatin. Although incidences of diarrhoea and skin rash were statistically higher in gefitinib containing arm but they were managble with proper intervention without causing treatment interruptions and delay. If the radiosensitizing ability of gefitinib can be proved definitively by further larger randomised trials it can be used in patients with poor performance status who are not eligible for intravenous cisplatin and also in cases where cisplatin is contraindicated like-renal compromise, pre-existing neuropathy, hearing abnormalities). Moreover, as gefitinib is a oral drug it is a more convenient treatment option for patients in comparison to intravenous cisplatin.

This study had it's limitations also -our sample size was small, so any statistical data have to be interpreted with caution. It was a single institutional study; hence result derived cannot be extrapolated on entire population. Entire study duration was about 18 months including patient accrual, intervention and assessment. So, the late toxicity profile, overall survival and quality of life related issues could not be assessed.

Conclusion

Gefitinib based concurrent radiotherapy is non-inferior to cisplatin based concurrent chemo-radiation for the treatment of locally advanced head and neck carcinoma with acceptable toxicity profile. However, to establish gefitinib based CTRT as an alternative and to know it's effect on overall survival and quality of life further large randomized studies with larger sample size and longer follow up are required.

Acknowledgement:

We acknowledge our head of the department of Radiotherapy for his guidance and all the Patients who participated in this study.

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Conflict of interest: Nil

Source of funding: Nil

Date received: Jun 30, 2022

Date accepted: Oct 28, 2022