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Response Evaluation of Radiotherapy With Concurrent Weekly Cisplatin Versus Concurrent Weekly Cisplatin Plus Daily Gefitinib In Locally Advanced Head-Neck Squamous Cell Carcinoma : An Extended Follow Up Study

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Abstract: *Head and neck cancer in india accounted for 30% of all cancers. approximately 90% of head and neck carcinoma over express epidermal growth factor receptor (EGFR). EGFR plays a role in predicting and modulating the response of HNSCC patients to radiation.Advanced Head and neck cancer has poor prognosis. We conducted Prospective study-*
Response evaluation of radiotherapy with concurrent weekly cisplatin versus concurrent weekly cisplatin plus daily geitinib in locally advanced head &neck cancer from2012 to 1015. Results of that study published in IOSR journal of dental and medical sciences on Volume 14 issue 2 feb. 16. in this study82 previously untreated patients of squamous cell carcinoma of head and neck cancer were divided into two groups- the cases group B (n=41) receiving gefitinib 500 mg OD started one week prior to radiation and continue till radiation completed. Both the groups receiving weekly cisplatin (30mg/m^2) with radiotherapy. The radiotherapy dose was 70 Gy /35 fractions, 2 Gy / fraction in both the groups. In group B, overall complete response (primary+nodal) was seen in 25 patients 60.97%. While in control group A 21 patients showed overall complete response i. e. 51.21 % patients which was statistically non significant. The most common adverse affects were skin rashes (p=0.009) and diarrhoea (p=0.02).The incidence of acute radiation dermatitis and mucositis was comparable in both the groups. We did extended follow up, up to 24 month & we shows better DFS in cases group B (34.5%) compared to group A(22.4 %).The present study shows that targeted therapy with gefitinib and chemoradiation is well tolerated with some enhanced, but manageable toxicities and has shown to improve locoregional control though further studies are needed.

Keywords: *chemoradiation, EGFR, gefitinib, squamous cell carcinoma head and neck, targeted therapy.*

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I. Introduction

Head and neck squamous cell carcinoma (HNSCC) is a challenging cancer to treat and cure. Prior to 2000, radiation alone was the predominant non-surgical treatment modality offered to patients with HNSCC. Concurrent chemoradiotherapy with or without surgery a multimodality approach is often been used for locally advanced head and neck cancer. The introduction of CRT was based on several phase III trials showing a survival benefit of adding chemotherapy to radiation vs radiation alone in locally advanced HNSCC[1-4].A meta-analysis of 87 trials conducted by Pignon et al from 1965 to 2000, which included 16485 patients, found an absolute survival benefit for chemotherapy of 4.5% at 5 years and an absolute benefit for concurrent CRT of 6.5% [5]. During the past decade, intense research has initiated a new era of cancer treatment, that of molecular therapeutics. The introduction of targeted therapy against the epidermal growth factor receptor (EGFR) pathway has improved survival in locally advanced squamous cell head and neck cancer (LAHNC). Today, the EGFR is a prime target for new anticancer therapy, with a broad range of inhibitors currently under investigation [6]. Monoclonal antibodies to EGFR, Cetuximab, Panitumumab, and Zalutumumab, have been the most investigated in SCCHN. A phase III randomized trial on concomitant radiation therapy plus cetuximab, an EGFR-specific antibody, found improved locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) in LAHNC patients[7]. In addition, low molecular weight tyrosine kinase inhibitors (TKIs) including Gefitinib (Iressa; AstraZeneca, Wilmington, Del) and Erlotinib (Tarceva; OSI Pharmaceuticals, Melville, NY/Genentech, South San Francisco, Calif). Newer "dual TKIs" that inhibit both EGFR and HER-2 have also been investigated. Gefitinib is an orally active selective inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK) an enzyme that regulates intracellular signaling pathways implicated in the proliferation and survival of cancer cells Gefitinib is slowly absorbed with peak level occurring 3.7 hours after dosing; steady state is achieved in 7-10 days[8]. Phase I studies indicated that gefitinib monotherapy was well

tolerated, generally with mild, manageable, and reversible adverse effects at doses up to 600 mg/d. The most frequent drug-related adverse events were acne-like skin rash in 46% to 64% of patients and diarrhea in 47% to 55% of patients[9,10]. Gefitinib was tested as a single therapeutic agent in phase II trials in patients with recurrent or metastatic squamous cell HNC. A daily dose of 500 mg was well tolerated, with grade 1 to 2 skin rash in 48% of patients, grade 1 to 2 diarrhea in 42% of patients, and grade 3 diarrhea in 6% of the patients. The observed response rate was 10.6%, and the disease control rate was 53%, with a suggestion that 500 mg seemed more active than 250 mg [11-13]. Changhu chen et al, conducted a phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer concluded that gefitinib (250 or 500 mg daily) was well tolerated with concomitant boost RT or concurrent chemoradiotherapy with weekly CDDP. protracted administration of gefitinib for up to 2 years at 250 mg daily was also tolerated well[14]. At the ASCO 2005 meeting, Cohen et al. presented the results from a phase II study, integrating gefitinib into a concurrent chemoradiation regimen in patients with advanced SCCHN, followed by gefitinib alone in the adjuvant setting. From the 69 patients accrued, only 42 subjects were evaluable for response, with a median follow-up of 10 months 16 patients had not yet been evaluated, the others were not evaluable for various reasons). Grade III-IV toxicities were consistent with previous chemoradiotherapy trials. Complete response rate (CR) was 88% (37/42), suggesting that this regimen might be promising for patients with advanced SCCHN[15]. Biswamit Bhattacharya et al, conducted a prospective randomised controlled trial of concurrent chemoradiation versus concurrent chemoradiation along with gefitinib in locally advanced squamous cell carcinoma of head and neck and found that 29.03% patients achieved complete response (CR) in the control arm while 36.67% patients achieved CR in the study arm (CR), but the difference was not significant statistically (P = 0.5255). Total number of patients achieving overall response (CR + PR) in control arm was 19 (61.29%) while it was 23 in the study arm (76.67%). However, the difference of overall response between the study arm and the control arm was not statistically significant (P = 0.1947). Disease free survival (DFS) rate at 1 year was 22.58% for the control arm and 33.33% for the study arm but it was not statistically significant (P = 0.515) and concluded that addition of Gefitinib to standard concurrent cisplatin based chemoradiation is well-tolerated, and in our study we found better overall response and DFS (at 1 year) with addition of Gefitinib to standard concurrent chemoradiation[16]. Krishnangshu choudhury et al evaluated the effectiveness of gefitinib as additional radiosensitizer to conventional chemoradiation for locally advanced non-metastatic squamous cell carcinoma of head and neck. in a prospective interventional randomized controlled study and found statistical difference in overall response between the two arms (p value 0.041) in favour of gefitinib arm (n=48) with overall response (ORR=CR+PR) of 91.6 % versus 69.5% in conventional cisplatin chemoradiation (n=46). Disease Free Survival favored the Gefitinib arm with Log Rank p value of 0.008. Gefitinib arm resulted in more grade 2 and 3 dermatitis, mucositis and diarrheal events. Adding Gefitinib to conventional chemoradiation in treatment of LAHNSCC improves ORR and DFS, with an increase in incidence of manageable toxicity [17].

II. Material And Methods

This prospective study was carried out at Department Of Radiotherapy NSCB Medical college Jabalpur in previously untreated histologically and cytologically proven patients locally advanced squamous cell carcinoma of head and neck (Stage III & IVA)**.** Age of patient 30-70 yrs, previously untreated with chemotherapy or radiation therapy with adequate haematology, liver, and kidney function test. Measurable or evaluable disease, Voluntarily given written informed consent, ECOG performance status 1 without evidence of metastasis were included in this study. Complete medical history and any significant past history or family history which attributed to malignancy was asked. Physical examination with an assessment of the patient's performance was done prior to the start of any protocol treatment.General physical, nutritional assessment, complete dental evaluation, clinical evidence of lymphadenopathy was done. Local examination included inspection, palpation finding of visible growth in oral cavity, Indirect laryngoscopy, rhinoscopy, direct laryngoscopy will be done as per required for respective site. Systemic examination of nervous, cardiovascular, respiratory and gastrointestinal system and exclusion of any evidence of distant metastasis was also done. Patients of both sexes were divided intoControl(group A) andcases (group B). In group A of 41 patients; the patient received Cisplatin 30mg/m^2along with radiotherapy, starting from day 1 of radiotherapy. In the group B of 41 patients; the patient received Gefitinib 500 mg, per oral, one week prior to radiotherapy followed by Cisplatin 30mg/m^2weekly along with radiotherapy, starting from day 1 of radiotherapy, till the completion of radiotherapy.The patients were treated on Cobalt-60 Teletherapy machine with a dose of 70Gy/35Fr/7 weeks. The shrinking field technique was used to spare spinal cord after 44Gy. Response and side effects evaluation was done weekly during treatment, at the end of RT and then monthly following completion of treatment. The response was assessed as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) [WHO criteria] at 4 weeks of completion of treatment. The primary end-point was complete response rate at 1 month post chemoradiotherapy and acute toxicity profile. The patients were followed upto 2

year(24 month), secondary end point was DFS { diseases free survival} .The two groups were compared using the chi square test to check whether they were statistically comparable in terms of outcome and toxicity profile.

III. Results

A total of 82 patients were available for final analysis; 69 male and 13 female. Fourty one patients were included in each group. The age of the patients was ranged from 30-70 years, 38 % were in age group of 30-49 yrs while 44 % in 50-70 yrs. Among 82 patients, 58 were from rural areas. Cancer of the oral cavity was the primary site in 35. 36 % of the patients, cancer of oropharynx, larynx and hypopharyx constituted 32. 92%, 28.04 % and 3.65% respectively. Majority of the patients i.e. 48.78 % were moderately differentiated while grade I and III/UD constituted 43.90 % and 7.31 % respectively. Stage III disease was present in 47. 56 % and stage IV disease was present in 52.43 % of patients. In group B complete response to primary disease was 65.8% and to nodal disease was 61% whereas in group A, we found that complete response of primary disease was 53.65% while complete response for nodal disease was 51.21 %. Partial primary and nodal response was seen more with control group patients i.e. 36.58% and 29.26% respectively. However an overall complete response of 60.97% was seen in study group B while it was 51.21 % in control group A. The average duration to complete the treatment is almost same (55 vs. 54 days) in both the groups indicating no significant toxicity-related treatment delay.Addition of Gefitinib to standard concurrent cisplatin-based chemoradiation was well-tolerated with no significant increase in acute radiation dermatitis or mucositis. The only acute toxicities that were significantly worse in the study arm were diarrhoea and Gefitinib-related acne-like skin rash occurred in 33 patients (80.48%), and all rashes were grade 1 or 2. However, it could be managed easily with supportive measures and did not contribute to delay in completion of treatment.). Disease free survival (DFS) rate at 2 year was 22.4 % for the control arm and 34.50 % for the study arm but it was not statistically significant ($P = 0.51$) and concluded that addition of Gefitinib to standard concurrent cisplatin based chemoradiation is well-tolerated, and in our study we found better overall response and DFS (at 2 year) with addition of Gefitinib to standard concurrent chemoradiation.

IV. Figures And Tables.

Table 1. Patient's characteristics

CHARACTER	TOTAL		control (GROUP A)		Case (GROUP B)	
	NO.	%	NO.	%	NO.	%
AGE (YRS)						
30-49	38	46.34	18	43.94	20	48.78
50-70	44	53.65	23	56.09	21	51.21
SEX						
FEMALE	13	15.85	6	14.63	7	17.03
MALE	69	84.14	34	82.92	35	85.36
LOCALITY						
RURAL	58	70.73	28	68.29	30	73.17
URBAN	24	29.26	13	31.70	11	26.82
SITE						
OC	29	35.36	14	34.14	15	36.58
OP	27	32.92	15	36.58	12	29.26
L	23	28.04	11	26.82	12	29.26
HP	3	3.65	1	2.43	2	4.87
GRADE						
I	36	43.90	17	41.46	19	46.34
II	40	48.78	22	53.65	18	43.90
III/UD	6	7.31	2	4.87	4	9.75
AJC STAGE						
III	39	47.56	20	48.78	19	46.34
IV	43	52.43	21	51.21	22	53.65

(laxmi et all, IOSR-JDMS volume 15 Feb. 2016)

Table 2. Response after radiation therapy in both treatment groups.

Table 2.1 Primary response.

Groups	CR	P value		PR	SD	PD	Total
Case	27			8	2	4	41
(group B)	65.8%			19.5%	4.9%	9.8%	100.0%
Control	22	0.192		15	1	3	41
(group A)	53.65%			36.58%	2.4%	7.3%	100.0%

(laxmi et all, IOSR-JDMS volume 15 Feb. 2016)

Table 2.2 Nodal response.

Groups	CR	P value	PR	SD	PD	Total
Case (group B)	25	0.20	8	3	5	41
	61.0%		19.51%	7.31%	12.1%	100.0%
Control (group A)	21		12	3	5	41
	51.21%		29.26%	7.31%	12.19%	100.0%

Table 2.3 Overall complete response (primary+ nodal).

	Case (group B)	Control (group A)	P value
Complete Response	25/41(60.97%)	21/41(51.21%)	0.46

Table 3. Acute toxicity profile.

GRADING	Case (group B)		Control (group A)		P value
RADIATIONDERMATITIS	NO.	%	NO.	%	
Grade I	8	19.51	9	21.95	0.32
Grade II	25	60.97	26	63.41	
Grade III	6	14.63	5	12.19	
Grade IV	2	4.87	1	2.43	
MUCOSITIS Grade I	4	9.75	5	12.19 12.8	0.48
Grade II	18	43.90	20	48.78	
Grade III	14	34.14	12	29.26	
Grade IV	5	12.19	4	9.75	
DIARRHOEA Grade I	8	19.51	2	4.87	0.02
Grade II	14	34.14	1	2.43	
Grade III	10	24.39	0	0	
Grade IV	0	0	0	0	
SKIN RASH	33	80.48	0	0	0.009

(laxmi et all, IOSR-JDMS volume 15 Feb. 2016)

Table 4. Disease free survival after 24 month

	DFS	P value	
Case (group B)	34.5	0.51	
Control (group A)	22.4		

V. Discussion And Conclusion

For many year, radiotherapy has been an acceptable option for patients with locoregional advance head and hancer. Treatment for early stage disease involves usually surgery and radiation therapy (RT). Locally-advanced tumors are best treated with concurrent chemotherapy to RT, either in the definitive setting or following surgery, according to each center's expertise.Although altered radiation fractionation and chemoradiotherapy had a favorable impact for advanced head and neck cancer patients, the outcome of patients presenting with stage III-IV SCCHN is still poor, with 5-year actuarial survival rates fluctuating between 30% and 40% in most trials [18]. The use of target therapy is an integral part of treatment of several malignancies. Various phase III and randomized phase II trials are going on to clinically investigate the molecularly targeted agents in locally advanced head and neck cancer. Keeping all these preceding studies in mind, we wished to evaluate whether addition of an EGFR-TKI can improve treatment outcome of our patients with locally advanced SCCHN. As we found in our study toxicities in both the groups were comparable in terms of radiation dermatitis and mucositis.Gefitinib does not seem to increase chemoradiotherapy-related mucositis and skin reaction found to be lower than those reported by Choudhury et al [17]. An exception to these findings was diarrhea, which occurred significantly more in the Gefitinib containing group. However, diarrhea could be adequately managed with supportive care and usually did not contribute to treatment delay. There was no grade 4 diarrhea and 10 cases of grade 3 diarrhea in the study group. Acne like skin rash was also seen in 33patients receiving gefitinib. Here we could find an overall complete response of 60.97% and 51.21% in group B and group A patients respectively.We could also observed that DFS rate at 2 year(24 month) was 22.4 % for the control arm and 34.50 % for the study arm.However, this encouraging result could not be validated with a statistical significance. The lack of statistical significance may probably be a reflection of the relatively small sample size of the present study, which was seen comparable to those reported for other concurrent chemoradiotherapy protocol in advanced head and neck malignancies[16]. It is found that administration of Gefitinib 500 mg once a day daily with Chemoradiotherapy is safe with a few manageable adverse effects. Patients have well tolerated Gefitinib 500mg once a day daily along with chemoradiotherapy and were well

compliant to its use. Discussing the above observations,it is quite obvious that addition of epidermal growth factor receptor inhibitor gefitinib to the concurrent chemoradiation has shown to improve locoregional control, over all response and DFS, with an increase in incidence of manageable toxicity in locally advanced head and neck squamous cell carcinoma. Concluding that using gefitinib with concurrent chemoradiation needs further clinical trial on large scale with a prolonged period of follow-up to validate those encouraging results and to clearly define the role of addition of Gefitinib to current standard of care in locally advanced squamous cell carcinoma of head and neck.

Reference

[1] Adelstein DJ, Li Y, Adams GL, Wagner H et al : An intergroup phase III comparison of standard radiation therapy and two schedules of ncurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol. 2003:21:92–982.

[2] Brizel DM, Albers ME, Fisher SR et al: Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998:338:1798–1804.

[3] Denis F, Garaud P, Bardet E et al : Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2004:22:69–76.

[4] Bourhis J, Sire C, Graff P et al: Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. Lancet Oncol. 2012:13:145–153.

[5] Pignon JP, le Maître A, Maillard E et al : Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients.Radiother Oncol. 2009:92:4–14.

[6] Baselga J: Targeting the epidermal growth factor receptor: a clinical reality. J Clin Oncol 2001: 19(Suppl): 41S-44S.

[7] Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567- 578:2006.

[8] Ang KK, Berkey BA, Tu X et al: Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res 2002;62:7350-6.

[9] Baselga J, Rischin D, Ranson M, et al: Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 20 : 4292 - 4302:2002.

[10] Herbst RS, Maddox AM, Rothenberg ML, et al: Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: Results of a phase I trial. J Clin Oncol 20: 3815 – 3825:2002.

[11] Cohen EE, Rosen F, Stadler WM, et al: Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 21:1980-1987:2003.

[12] Cohen EE, Kane MA, List MA, et al: Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Clin Cancer Res 11:8418-8424:2005.

[13] Cohen EE: Role of epidermal growth factor receptor pathway-targeted therapy in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 24:2659-2665:2006.

[14] Changhu Chen, Madeleine Kane, John Song et al: Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer .J Clin Oncol 2007:25:4880-6.

[15] Cohen EE, Haraf DJ, Stenson KM et al: Integration of gefitinib (G) into a chemoradiation (CRT) regimen, followed by G adjuvant therapy in atients with locally advanced head and neck cancer (HNC): A phase II trial. JClin Oncol 2005:23 (Suppl): 501s.

[16] Biswamit Bhattacharya, Santanu Pal, Bitoti Chattopadhyay et al 2014 : A prospective randomised controlled trial of concurrent chemoradiation versus concurrent chemoradiation along with gefitinib in locally advanced squamous cell carcinoma of head and neck. Clinical cancer investigation journal.Vol : 3:146-152.

[17] Krishnangshu Bhanja Choudhury, Shyam Sharma1, Chandrani Mallick et al: Effectiveness of gefitinib as additional radiosensitizer to conventional chemoradiation for locally advanced non-metastatic squamous cell carcinoma of head and neck. prospective interventional randomized controlled study. Journal of biology, agriculture and healthcare. Vol 2:No.1: 2012

[18] Licitra L, Locati LD, Bossi P: head and neck cancer. Ann Oncol 2004:15 (Suppl 4) : iv 267-iv 273.

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